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(54) Title: DESIGN AND SYNTHESIS OF OPTIMIZED LIGANDS FOR PPAR

(57) Abstract: This invention provides new chemical entities useful for treating a variety of clinical disorders including those that are influenced by the activity of peroxisome proliferator activated receptors (PPAR) including PPARalpha, PPARdelta, and or PPARgamma. The structures of the compounds and methods to design, make and use the compounds are provided. Tautomers, stereoisomers and derivatives of the subject compounds, and pharmaceutically acceptable salts and solvates thereof, and their uses in the treatment of metabolic, inflammatory, autoimmune, proliferative and degenerative diseases are also provided.

DESIGN AND SYNTHESIS OF OPTIMIZED LIGANDS FOR PPAR

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority to U.S. Provisional Application No. 60/278,097, filed March 23, 2001, and U.S. Provisional Application No. 60/283,774, filed April 13, 2001, the contents of which are incorporated by reference herein in their entirety.

FIELD OF THE INVENTION

[0002] This invention relates to the field of rational drug design. Specifically the invention relates to compounds that interact with peroxisome proliferator activated receptors (PPARs) and methods for their design and synthesis.

BACKGROUND OF THE INVENTION

[0003] Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear receptor superfamily of ligand-activated transcription factors. Three subtypes of PPARs have been cloned from the mouse and human: i.e., PPARalpha, PPARgamma and PPARdelta. In humans PPARgamma and PPARalpha are differentially expressed in organs and tissues (Willson *et al. J. Med. Chem.* 43:527-50 (2000) Nuclear receptors like PPAR possess DNA binding domains (DBDs) that recognized specific DNA sequences (called response elements) located in the regulatory regions of their target genes Mangelsdorf et al *Cell* 83:835-839 (1995)). Activation of PPARs modulates the expression of genes containing the appropriate respective peroxisome proliferator response elements (PPRE) in its promoter region. PCT WO/25226.

[0004] PPARgamma consists of three forms, PPARgamma1 which is broadly expressed in most tissues, PPARgamma2, is more restricted to adipose (white fat and brown fat) tissue, and PPARgamma3. PPARgamma3 is confined to adipose tissue, macrophages and colonic epithelium in rodent and human tissues (Mangelsdorf, and

Evans *Cell* (1995) 83:841-850; Spiegelman. *Diabetes* (1998) 47:507-514; Willson et al., *J. Med. Chem.* (2000) 43:527-550). The distribution of the other PPARs also varies in different tissues. Throughout this writing PPAR refers to any of these isoforms, subtypes or combination thereof. PPARgamma is functionally involved in intermediary metabolism of cells and tissues that express this nuclear receptor.

[0005] PPARgamma and PPARalpha and PPARdelta are differentially expressed in different organs and tissues. Activation of PPARgamma and/or PPARalpha and/or PPARdelta modulates the expression of genes involved in: 1) glucose and lipid metabolism, 2) the regulation of cell growth, differentiation and regulation of the mitotic cycle, 3) the inflammatory response in cells of the immune system, 4) suppression of components of the immune system that become activated in pathological situations, and 5) regulation of apoptosis (programmed cell death) in a variety of cell types. Impairment in these processes lead to pathophysiolgical conditions involving metabolic (endocrine) dysfunction, proliferative diseases, inflammatory diseases and degenerative diseases. (Pershadsingh, *Expert Opin. Investig. Drugs* 8(11):1859-1872 (1999)).

[0006] The precise mechanism whereby ligand activation of PPARs lead to changes in gene expression is poorly understood. Full activation of PPARgamma and/or PPARalpha and/or PPARdelta requires its functional dimerization with the retinoid X receptor (RXR) to form PPARgamma/RXR or PPARalpha/RXR or PPARdelta/RXR. The endogenous ligand for RXR is 9-cis-retinoic acid. Nutrient retinoids and retinoic acid such as 13-all-trans-retinoic acid are converted to 9-cis-, 11-cis-, or 13-cis-retinoic acid by ubiquitous intracellular isomerases (Warrell Jr *et al.*, *New Engl. J. Med.* 329(3):177-189 (1993)). The full spectrum of genes that can be regulated by PPARalpha or PPARgamma or PPARdelta or their respective heterodimers remain to be defined.

[0007] PPAR agonists have been shown to inhibit the expression of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-alpha), IL-1, IL-2, IL-6 in cells of the immune system including, T lymphocytes, B lymphocytes, monocytes, monocyte/macrophages, and splenocytes. PPARgamma agonists tend to suppress inflammation mediated by Th1 lymphocytes (Marx et al., *J. Immunol.* 164:6503 (2000);

Padilla et al., *Ann N. Y. Acad. Sci.* 905:97 (2000); Clark et al., *J. Immunol.* (2000) 164:1364; Yang et al., *J Bio.l Chem* .(2000) 275:4541). However, the anti-inflammatory effects of PPARgamma are controversial. It has been reported that PPARgamma activators are not useful for the treatment of acute inflammation in db/db diabetic mice (Thieringer et al., *J. Immunol.* (2000) 164:1046). Thiazolidinedione-treated db/db mice challenged with lipopolysaccharide, a potent pro-inflammatory agent, displayed no suppression of cytokine production. Rather, their blood levels of TNF-alpha and IL-6 were elevated beyond the levels observed in control mice.

[0008] PPAR agonists have also been shown to inhibit proliferation and promote differentiation of a variety of normal and neoplastic cell types. Spiegelman et al., PCT/US97/22879, published June 18, 1998, disclose methods for inhibiting proliferation of PPARgamma-responsive hyperproliferative cells by using PPARgamma agonists; numerous PPARgamma agonists are disclosed by Spiegelman et al., as well as methods for diagnosing PPARgamma-responsive cells. The method relates to superior efficacy of PPAR activators or co-activators of various subtypes in: 1) promoting apoptosis of neoplastic cells, 2) systemic anti-inflammatory effect by suppressing Th1-mediated inflammatory cytokines and promoting Th1 to Th2 phenotypic transition resulting in of immunosuppression, leading to prevention, amelioration or reversal of degenerative diseases.

[0009] Examples of diseases susceptible to the immunosuppressive effects of activators of PPARgamma, or PPARalpha, or PPARdelta, or co-activators of any of these subtypes are: inflammatory skin diseases (e.g. psoriasis, atopic dermatitis, eczema, acne vulgaris, and other dermatitides), neurodegenerative diseases (e.g. multiple sclerosis, Alzheimer's disease, Parkinson's disease), cardiovascular diseases (e.g. atherosclerosis, venous and arterial occlusive diseases, restenosis after invasive procedures, cardiomyopathy, myocardial fibrosis, congestive heart failure), pulmonary disorders (asthma, chronic obstructive pulmonary disease), angiogenesis and neovascularization in neoplastic and other diseases. The immune system includes T lymphocytes, B lymphocytes, monocytes, macrophages, monocyte/macrophages, macrophage-like cells

(e.g. astrocytes in the brain, retinal pigmented epithelial cells in the retina), cells of myeloid origin in any tissue, in particular the bone marrow (stem cells, pre-promyelocytes, promyelocytes, myelocytes, granulocytes, plasma cells, mast cells, basophils, polymorphonuclear cells, eosinophils).

[0010] In humans, PPARgamma and PPARalpha and PPARdelta are differentially expressed in organs and tissues (Willson et al., *J. Med. Chem.* (2000) 43 (4):527-50). This heterogeneous distribution is particularly evident in the complex structure of the eye (Braissant et al., *Endocrinology* (1996) 137:354-366; Pershadsingh et al., Proceedings of the Society for Neurosciences. Miami Beach, USA,1999). It can be difficult to predict what cells and diseases are influenced by PPARgamma and/or PPARalpha activity and/or PPARdelta due to the varied tissue distribution of expression of the various PPAR subtypes and the varied amounts of their respective proteins in various cells (Escher *et al., Endocrinology* 142(10):4195-202 (2001); Braissant O, Wahli W, *Endocrinology* 139(6):2748-54 (1998)). Further, some PPAR subtypes are expressed in some cells while in a normal state, but not expressed or expressed to a lesser or greater degree by the abnormal cells, or visa versa. Specifically, PPARgamma and PPARalpha are differentially expressed in diseased versus normal cells. For example PPARgamma is expressed in normal human keratinocytes but not in normal human dermal fibroblasts (Ellis et al., *Arch. Dermatol.* (2000) 136:609-616). PPARgamma has been shown to be expressed in a greater amount in level was increased in the subcellular cytosolic fraction of Alzheimer's disease brains, compared to control brains (Kitamura et al., *Biochem. Biophys. Res. Commun.* 1999; 254:582-586).

[0011] The activity of PPARgamma or PPARalpha or PPARdelta depends on the degree to which the receptor protein is phosphorylated and/or on the conformation of the receptor. It has been proposed that phosphorylation could alter interactions with protein cofactors of PPARgamma which act as corepressors or coactivators. Nuclear receptors function as "ligand-gated" platforms for the assembly of these cofactors into large protein complexes on specific DNA sequences (Spiegelman *Diabetes* (1998) 47:507-514). Some of these coactivator proteins (CBP/p300, SRC1, pCAF) have histone acetyltransferase

activity that functions to "open" the configuration of chromatin, allowing more efficient transcription. Others act as deacetylases which oppose the effects of acetyltransferases. Similar arguments apply to PPARalpha modulation of gene transcription. One theoretical problem is whether the nuclear receptor coactivators or corepressors identified to date are selective for particular PPAR receptors, and this remains unknown (Spiegelman BM. *Diabetes* (1998) 47:507-514). In fact, these coactivators or corepressors have multiple modes of action and hence, it is not clear which cofactors are more important for the function of any particular receptor (Puigserver et al., *Science* (1999) 286:1368-1371. It is also not obvious how the tremendous specificity of biological actions of the individual nuclear receptors are generated (Spiegelman, *Diabetes* (1998) 47:507-514). Consequently, the full spectrum of nuclear cofactors that regulate the transcriptional activity of PPARgamma and/or PPARalpha or PPARgamma/RXR and/or PPARalpha/RXR remains to be defined. The way in which a tissue expressing PPARgamma and/or PPARalpha and/or PPARdelta may respond to a particular ligand, and a pathological state will be attenuated, arrested, accentuated or worsened by said ligand can vary for example in the case in which a single ligand activates both PPARgamma and PPARalpha to similar degrees, i.e. a co-activator of both PPARgamma and PPARalpha (or similarly, both PPARgamma and PPARdelta or PPARalpha and PPARdelta).

[0012] Until recently, the genes regulated by PPARs were those believed to be predominantly associated with lipid and glucose metabolism. Recently, an immunomodulatory role for PPARgamma and PPARalpha has been described (Shu et al., *Biochem. Biophys. Res. Commun.* (2000) 267(1):345-9). The immunomodulatory/immunological mechanisms underlying inflammatory diseases mediated by or related to T lymphocyte activation are not well understood. Immunosuppressive agents capable of blocking various steps of the immune response have been utilized to prevent, ameliorate or reverse the inflammatory process, often by downregulating critical nuclear transcription factors that, in turn, regulate the expression

of genes encoding inflammatory cytokines. Production of inflammatory cytokines occur in hypertriglyceridemic and other dyslipidemic states, e.g. diabetes mellitus.

[0013] Both PPARalpha and PPARgamma activators have been shown, independently, to suppress expression of these inflammatory regulators, inhibit proliferation and promote apoptosis of pathological cellular phenotypes. Paradoxically and unexpectedly, the opposite case occurs wherein the therapeutic compositions are administered in the treatment of degenerative disease such as multiple sclerosis (a neurodegenerative) or retinopathies and retinitis (retinal degenerative diseases), in which prevention of apoptosis is the operative mechanism. Therefore, in these disease states, activation of PPARalpha and PPARgamma by suppressing transcription of inflammatory cytokines, prevents apoptosis of the target cell and promotes survival of the non-pathological cellular phenotype. For example, in the case of multiple sclerosis, an autoimmune T lymphocyte-mediated disease, the target cell sustaining the pathological insult is the myelin sheath (oligodendrocyte) in the central nervous system. The pathological cellular phenotypes are amnestic T lymphocytes lacking immune recognition of oligodendrocytes, and inappropriately activated microglia, resulting in inappropriately activation and production of harmful inflammatory cytokines (Zhang et al., *Mult. Scler.* (2000) 6:3-13). PPARgamma activation can inhibit neuronal apoptosis and promote neuronal protection through the upregulation of neuronal apoptosis inhibitory protein (Magun et al., *Diabetes* (1998) 47:1948-52). Indeed, PPARgamma activation protects cerebellar granule cells from cytokine-induced apoptotic cell death (Heneka et al., *J. Neuroimmunol.* (1999) 100:156-68). Moreover, PPARalpha has been shown to suppress inflammatory cytokines and nuclear factors in monocyte/macrophages. A similar mechanism involving suppression of inflammatory cytokine production by microglia would prevent oligodendrocyte apoptosis. Finally, combined PPARalpha/PPARgamma activation could promote Th1/Th2 differentiation as a final common pathway to inhibit apoptosis of the non-pathological phenotype and promotion of neuronal protection (Giorgini et al., *Horm. Metab. Res.* (1999) 31:1-4; Clark et al., *J. Immunol.* (2000) 164:1364-71).

[0014] PPARgamma interactions with co-activators and co-repressors tend to be ligand-specific. For example, the natural PPARgamma ligand, 15-deoxy-delta-12,14-prostaglandin J2 can induce the receptor-ligand complex to interact with the cofactors: SRC-1, TIF2, AIB-1, p300, TRAP220/DRIP205, whereas, under the same conditions the anti-diabetic thiazolidinedione, troglitazone, a synthetic PPARgamma ligand does not. Therefore, ligand binding may alter PPARgamma structure in a ligand-type specific way, resulting in distinct PPARgamma-coactivator interactions (Kodera et al., *J. Biol. Chem.* (2000) 275(43):33201-33204. By analogy, a similar mechanism would provide ligand-specific control of gene expression in the case of PPARalpha activation or PPARdelta activation.

SUMMARY OF THE INVENTION

[0015] This invention involves the discovery of new chemical entities that have utility for treating a variety of clinical disorders including those that are influenced by the activity of peroxisome proliferator activated receptors (PPAR) including PPARalpha, PPARdelta, and or PPARgamma (the term "subtypes" is used herein to refer to the various types of PPARs including PPARalpha, PPARdelta, and PPARgamma). The invention also involves the surprising finding that the compounds are potent activators of peroxisome proliferator activated receptors. Compounds and methods on how to design, make and use the compounds are described herein. The invention also describes tautomers, stereoisomers and derivatives of the subject compounds, and pharmaceutically acceptable salts and solvates thereof, and their uses in the treatment of metabolic, inflammatory, autoimmune, proliferative and degenerative diseases.

[0016] This invention describes novel compounds that activate PPARs and that are useful for the treatment of clinical disorders that are influenced by the activity of various PPAR subtypes. Methods of this invention include how to make and use the compounds for the treatment of a T lymphocyte-related or autoimmune, inflammatory, proliferative, dystrophic, degenerative diseases, such as those involving ischemia, angiogenesis, atherosclerosis, increased cell proliferation, immune mediated inflammation,

neovascularization, and or apoptosis, by administering to a human or animal in need of treatment an effective amount of a PPARgamma activator, or a PPARalpha activator, or a co-activator of both PPARgamma and PPARalpha, or a PPARdelta activator to attenuate, reverse, prevent, ameliorate, or stop the disorder. Provided are thiazolidinedione and non-thiazolidinedione ligands, their esters, salts, solvates and tautomers and various derivatives of these ligands.

[0017] In another aspect, provided are compounds that bind to nuclear receptors by forming a disulfide linkage between a thiol group in the ligand and a cysteine residue in the receptor. In another aspect, the invention provides compounds containing a halogen-substituted pyridine group that can form a covalent linkage with a cysteine residue in a particular nuclear receptor. Typically, the substituted pyridine group is located at the tail-end of the molecule.

[0018] In another aspect, this invention discloses compounds with molecular characteristics that enhance their binding affinity to the ligand-binding domain (LBD) of PPAR nuclear receptors, wherein the compound has structural features and constraints that enhance (optimize) receptor binding in order to maximize transactivation or deactivation. Preferred ligands contain a polar headgroup that promotes high affinity binding to activating site of the of the PPAR LBD, leading to efficient PPAR transactivation, i.e., the binding of agonist ligands to the receptor resulting in changes in the expression level of mRNAs encoded by PPAR target genes. Receptor deactivation or antagonism may occur when it is covalently bound, but the headgroup fails to effectively engage the activating site of the LBD, resulting in failure of the ligand to transactivate the nuclear receptor.

[0019] Pharmaceutical compositions comprising compounds disclosed herein, as wells as salts solvates, esters, tautomers or stereoisomers are provided. Optionally, the composition further includes a pharmaceutically acceptable excipient.

[0020] Also provided is a method for treating a peroxisome proliferator activated receptor (PPAR) mediated disease, or risk factor, wherein the method includes administering to a human or an animal in need thereof, a therapeutically effective amount

of a compound according to any one of the compounds described herein. Optionally, the compound is a PPARgamma activator, PPARalpha activator, or PPARdelta activator.

[0021] Also provided is a method wherein the compound is administered in combination with a natural or a synthetic therapeutic compound.

[0022] In one embodiment, a method for designing a compound which is an L-shaped ligand molecule capable of binding to at least one of PPAR-α, δ, and γ, is provided. In one embodiment, the method includes:

identifying at least one ligand binding domain (LBD) in a selected PPAR;

selecting at least a first chemical group capable of binding to the LBD of the PPAR;

selecting a second chemical group capable of interacting with at least one amino acid in the LBD to have an effect on transcription mediated by the PPAR; and

determining a formula of an L-shaped ligand molecule wherein the L-shaped ligand molecule comprises a first leg section and a second leg section, the first leg section comprising the first chemical group that binds the LBD of the PPAR, and the second leg section comprising the second chemical group which interacts with an amino acid on the PPAR, and further wherein the first and second leg sections of the L-shaped ligand molecule are connected at an elbow atom common to both legs such that the first and second legs are capable of orienting in a conformation which creates an angle of about 80 to 110 degrees between the first and second legs.

[0023] Optionally, the method can also include synthesizing the L-shaped ligand molecule and determining its ability to bind to at least one of PPAR-α, δ, and γ.

[0024] The LBD of the PPAR may comprise a cysteine residue. The first chemical group may comprise a thiol which is capable of forming a disulfide linkage with the cysteine residue in the LBD. The first leg section of the L-shaped ligand molecule may comprise a lipophilic terminal group that promotes binding to an active site of a PPAR isoform. The first chemical group may comprise a halogen-substituted pyridine group which which is capable of forming a covalent linkage with the cysteine residue in the LBD.

[0025] Interaction of the amino acid of the LBD with a second chemical group on the L-shaped ligand molecule may be via hydrogen bonding. The compound may be an activating ligand that binds the PPAR, and a second chemical group on the L-shaped ligand molecule may interact with a Tyr473 residue on the PPAR.

[0026] The L-shaped ligand molecule may be an inactivating ligand that binds the PPAR, wherein the second chemical group on the L-shaped ligand molecule does not interact with a Tyr473 residue on the PPAR. Further, an L-shaped ligand molecule may be designed for optimal binding to a PPAR LBD by determining at least one geometric constraint on the ligand. Optionally, the L-shaped ligand molecule is an agonist of the PPAR or an antagonist of the PPAR.

[0027] In another embodiment, a computer-assisted method for designing a compound which is an L-shaped ligand molecule specific for at least one of PPAR-α, δ, and γ, using a programmable computer including a processor, an input device, and an output device is provided. The method comprises in one embodiment:

(a) inputting into the programmable computer, through the input device, data including the identity of at least one ligand binding domain (LBD) in the selected PPAR;

(b) determining, using the processor, the identity of at least a first chemical group capable of binding to the LBD of the PPAR;

(c) determining, using the processor, the identity of a second chemical group capable of interacting with at least one amino acid in the LBD to have an effect on transcription mediated by the PPAR; and

(d) outputting, to the output device, the formula of an L-shaped ligand molecule wherein the L-shaped ligand molecule comprises a first leg section comprising the first chemical group which binds the LBD of the PPAR, and a second leg section comprising the second chemical group which interacts with an amino acid on a PPAR, and further wherein the first and second leg sections of the ligand molecule are connected at an elbow atom common to both leg sections, such that the first and second leg sections are capable of orienting in a conformation with an angle of about 80 to 110 degrees with

respect to each other. The L-shaped ligand molecule may be designed for optimal binding to a PPAR LBD by determining at least one geometric constraint on the compound.

[0028] Another method for designing an L-shaped ligand molecule capable of binding to at least one of PPAR-α, δ, γ is provided. The method comprises identifying an L-shaped molecule comprising a first leg section L_1 and a second leg section L_2 wherein the longitudinal axes of L_1 and L_2 are connected by a shared elbow atom c, wherein:

(a) L_1 and L_2 are capable of assuming approximately linear extended conformations wherein L_1 and L_2 are independently each about 9-13 Å in length;

(b) leg sections L_1 and L_2 are connected at the elbow atom c such that the first and second leg sections are capable of orienting in a conformation which creates an angle of about 80 to 110 degrees between the first and second legs;

(c) a terminus of L_1 contains an acidic moiety of pK_a between 4 and 6, and has acceptor atoms capable of hydrogen-bonding; and

(d) a terminus of L_2 contains a moiety selected from the group consisting of a basic moiety, an acidic moiety, functional groups of varying polarity, and a neutral hydrocarbon moiety. Optionally, the angle between leg sections L_1 and L_2 is about 90 degrees.

[0029] The L-shaped ligand molecules identified by the method described herein are optionally synthesized, and optionally tested for an ability to bind at least one of PPAR-α, δ, and γ or PPAR isoforms. Optionally, L_1 and L_2 independently are about 11-12 Å. Optionally, L_1 is about 11.1 Å and L_2 is about 11.4Å.

[0030] Optionally, an L-shaped ligand molecule is designed that is capable of assuming a configuration wherein a torsional dihedral angle is generated by atoms a-b-c-d of the molecule, wherein atoms a and b are adjacent connected atoms in leg section L_1, atom b is connected to elbow atom c, and atom c is connected to atom d in leg section L_2, further wherein:

a dihedral angle between a plane containing the atoms a, b and c and a plane containing the atoms b, c and d is between 45 and 85 degrees; and

a distance from an L_1 head group acid proton to an apex of the dihedral angle is at least about 3.5Å.

BRIEF DESCRIPTION OF THE DRAWINGS

[0031] Figure 1 illustrates an overlay of compound **20** (DOCKed with PPAR-γ, protein omitted) with compound **56**.

[0032] Figure 2 illustrates acidic head group (Z in Case I) replacements for the thiazolidine-2,4-dione in PPAR Ligand Design.

[0033] Figure 3 illustrates examples of various combinations of R and Z groups that are possible for Case 1.

[0034] Figure 4 is a schematic representation of how a large ligand substituent in proximity to Ile-341 creates a significantly unfavorable thermodynamic interaction.

[0035] Figure 5 shows the structure of exemplary binding ligands.

[0036] Figure 6 shows the structure of exemplary ligands of PPAR.

DETAILED DESCRIPTION OF THE INVENTION

[0037] As used herein, the term "alkyl" includes a branched or unbranched hydrocarbon chain, for example, including about 1 to about 8 carbons, such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, octa-decyl and 2-methylpentyl. Alkyl can be optionally substituted with one or more functional groups which are attached commonly to such chains, such as hydroxyl, bromo, fluoro, chloro, iodo, mercapto or thio, cyano, alkylthio, aryl, carboxyl, carbalkoyl, alkyl, alkenyl, nitro, amino, alkoxyl, amido, and the like to form substituted alkyl groups such as trifluoro methyl, 3-hydroxyhexyl, 2-carboxypropyl, 2-fluoroethyl, carboxymethyl, cyanobutyl and the like. The term "cycloalkyl" includes a cyclic alkyl.

[0038] The term "heteroalkyl" includes a branched or unbranched hydrocarbon chain having one or more heteroatoms in between carbon atoms. The term "heterocycle" includes a hydrocarbon chain forming one or more rings and having one or more

heteroatoms in the ring. Alkylheterocycles include alkyl groups attached to heterocycles. Alkylheteroaryls include alkyl groups attached to heteroaryls. Heteroalkyl and heterocyclic groups may be substituted for example as described for alkyl groups.

[0039] The term "aryl" includes a chain of carbon atoms which form at least one aromatic ring having for example between about 6-14 carbon atoms, such as phenyl, naphthyl, and the like. The aryl optionally may be substituted with one or more functional groups which are attached commonly to such chains, such as hydroxyl, bromo, fluoro, chloro, iodo, mercapto or thio, cyano, cyanoamido, alkylthio, heterocycle, aryl, heteroaryl, carboxyl, carbalkoyl, alkyl, alkenyl, nitro, amino, alkoxyl, amido, and the like. Aryl and substituted aryl groups include biphenyl, iodobiphenyl, methoxybiphenyl, anthryl, bromophenyl, iodophenyl, chlorophenyl, hydroxyphenyl, methoxyphenyl, formylphenyl, acetylphenyl, trifluoromethylphenyl, trifluoromethylthiophenyl, trifluoromethoxyphenyl, alkylthiophenyl, trialkylammoniumphenyl, amidophenyl, thiazolylphenyl, oxazolylphenyl, imidazolylphenyl, imidazolylmethylphenyl, and the like.

[0040] The term "heteroaryl" includes a ring system including one or more aromatic rings and containing one or more heteroatoms, N, O, or S, in the aromatic ring. Heteroaryl groups can be unsubstituted or may be substituted for example as described for alkyl groups.

[0041] The term "acyl" refers to moiety of the formula --C(O)R', wherein R' is for example alkyl, aryl, heteroaryl, heterocyclic; such as formyl, acetyl, propionyl, or butyryl.

[0042] This invention relates to the synthesis and uses of new compounds to treat diseases of multiple organ systems, including those contained in the cardiovascular system, pulmonary system, integumentary system, skeletal system, bone marrow, immune system, central and peripheral nervous system, endocrine and exocrine glands, urogenital system, and gastrointestinal system, and other tissues that express peroxisome proliferator-activated nuclear receptors (PPARs), including PPARalpha, gamma and delta, a family of nuclear transcription factors. PPARγ includes the γ_1, γ_2 or γ_3 isotypes or a

combination of all three isotypes. PPARs are nuclear receptors which naturally bind to fatty acids and which have been implicated in adipocyte differentiation (Perlmann & Evans, *Cell*, 90:391-397 (1997)).

[0043] This invention further relates to modulating the activity of nuclear transcription factors or other factors that are involved in the promotion of diseases involving derangements in: lipid and carbohydrate metabolism, inflammation, proliferation, differentiation, pathological activation of lymphocytes, apoptosis, nitric oxide formation, matrix metalloproteinases (MMPs), and tissue inhibitors of MMPases (TIMPs) by pharmaceutically acceptable forms including salts and solvates of the compounds described herein. PPARalpha has been shown to have substantial anti-lipemic and anti-dyslipidemic properties which contribute to their anti-inflammatory and anti-apoptotic activities, and their efficacy in the treatment of vast array of pathologies and diseases (see Tables I through X inclusive).

[0044] Another aspect of this invention relates to methods and uses of PPARgamma activators, or PPARalpha activators, or PPARdelta activators or co-activators of any combination of the PPAR subtypes, for treating inflammatory immune-mediated diseases by suppressing acute and chronic inflammatory production of inflammatory cytokines, and by promoting phenotypic transition of lymphocytes from the Th1 to the Th2 phenotype.

[0045] In another aspect, this invention relates to the subject compounds in the treatment of the diseases listed in Tables I through Table X, administered as either as a single agent, or in combination with a natural or synthetic compounds. Such compounds include agonists for PPARalpha, PPARdelta, PPARgamma, retinoid X receptor (RXR), vitamin D receptor (VDR), glucocorticoid receptor (GR), Liver X receptor (LXR) or LXR/RXR (e.g. an oxysterol (22(R)-hydroxycholesterol, 25-hydroxycholesterol, 7a-hydroxycholesterol, 24-hydroxycholesterol, 27-hydroxycholesterol, 40-hydroxycholesterol, 20,22-dihydroxycholesterol, and 20(S)-hydroxycholesterol, or a synthetic, synthetic nonsteroidal LXR-selective agonist (represented by T0314407 and T0901317, Schultz *et al.*, *Genes Dev.*14(22):2831-8 (2000)), Farnseoid X receptor (FXR)

or FXR/RXR (e.g. farnesol, chenodeoxycholic acid, a bile acid), and beta3-adrenoceptor. The compounds of this invention can also be, administered as either a single agent, or in combination with a natural or synthetic compounds that include inhibitors for 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (e.g. atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, simvastatin, rosuvastatin), and cholesterol ester transfer protein (CETP) (e.g. a substituted-1,2,3,4-tetrahydroquinoline). The compounds of this invention can also be administered as either a single agent, or in combination with a natural or synthetic compounds that can include a pharmacological agent that increases the expression or upregulates the ATP-binding cassette protein 1 (ABC1), calcineurin inhibitor (e.g. cyclosporine A, tacrolimus, sirolimus), an anti-hypertensive angiotensin converting enzyme (ACE) inhibitor (e.g. benazepril, captopril, cilazapril, enalapril, enalaprilat, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril), or an anti-hypertensive angiotensin receptor blocker (ARB)(e.g. losartan, valsartan, irbesartan, candesartan), telmisartan, eprosartan).

[0046] Another aspect of this invention relates to methods for screening libraries of compounds to determine which are the best candidates among the subject compounds for use in the practice of this invention.

[0047] In another aspect, the present invention generally relates to the treatment of T lymphocyte-related diseases that involve activation of nuclear factor of activated T lymphocyte NFAT, NF-kappaB or AP-1, inappropriate activation of nuclear transcription factors that regulate the transcription of genes encoding inflammatory cytokines, inappropriate transcription of genes encoding said inflammatory cytokines, and increased secretion and activity of said inflammatory cytokines. Examples of cytokines relating to this invention include, but are not limited to interferon-gamma(INFgamma), tumor necrosis factor-alpha (TNF-alpha), and a variety of the inflammatory and immunomodulatory interleukins (Chinetti et al. J. Biol. Chem. 1998; 273:25573-25580; Escher and Wahli, Mutat. Res. 2000; 448:121-138; Ricote et al., J. Leukoc. Biol. 1999; 66:733-739; Rocchi and Auwerx, Ann. Med. 1999; 31:342-351). This invention further relates to the prevention or treatment of disorders of inflammatory and

immunomodulatory responses of the immune system involving: T helper (T_H), T suppressor (T_S), Th1 and Th2 lymphocytes, natural killer (NK) and other T cell subsets; the T cell receptor (TCR) and cellular signal transduction pathways initiated by TCR activation; the major histocompatibility complex (MHC) and cellular transduction pathways initiated by MHC activation. Inflammatory cytokine produced by T lymphocytes include but not limited to: IL-1alpha, IL-1beta, IL-2, IL-4, IL-6, IL-8, IL-9, IL-11, IL-12, IL-15, IL-16, IL-18, TNF-alpha or INFgamma. Lymphoid-specific and other ubiquitous transcription factors include but are not limited to NFAT, NF-IL2A, activated protein-1 (AP-1), nuclear factor-kappaB (NF-kappaB), Oct1, CD28; signal transducers and activator of transcription (STATs) which regulate DNA gene promoter sequences; oncogenes (e.g. c-myc, c-jun, c-fos), CD40/CD40L.

[0048] In another aspect, the present invention is directed to compounds including positional and optical isomers of the subject compounds having one or any combination of the following properties: anti-inflammatory activity, e.g. by blocking production of inflammatory cytokines; prevention of programmed cell death (apoptosis), e.g. in degenerative diseases; induction of programmed cell death (apoptosis), e.g. in neoplastic cells or malignancies; anti-proliferative activity by blocking mitosis or otherwise interrupting the cell cycle; anti-proliferative activity by promoting differentiation; anti-thrombotic or blood clot dissolving activity, e.g. inhibition of thrombin or GP IIb/IIIa; inhibitory effect on nitric oxide synthase (iNOS); inhibitory effect on matrix metalloproteinases (MMPase) e.g gelatinases, collagenases, stromelysins, matrilysins, and/or their respective pro-enzymes; inhibition of the nuclear receptor, nuclear factor-kappaB (NF-kappaB); inhibition of the nuclear receptor, activated protein-1 (AP-1); and inhibition of the of the nuclear receptor, nuclear factor of activated T lymphocytes (NFAT).

[0049] In another aspect, the present invention generally relates to the treatment of diseases involving inappropriate apoptosis or inappropriate activation of the apoptotic programmed cell death pathway. Apoptotic regulators which malfunction resulting in pathological diseases or conditions include: fas/fasL, Apo-1/CD95, FADD, TRADD,

Apo2L/TRAIL, the TNF receptor, caspases (in particular caspase-3), inducible nitric oxide (iNOS) gene transcription and nitric oxide production. Several of these components are regulated primarily or secondarily by PPARgamma and/or PPARalpha activation. (Delerive, et al., *J. Endocrinol.* 169(3):453-9 (2001))

Synergistic Activation by PPARalpha and PPARgamma Ligands

[0050] Activation of both PPARalpha and PPARgamma have effects on metabolic risk factors that lead to chronic systemic inflammation that can result in diabetes, atherosclerosis, congestive heart failure, ulcerative colitis, rheumatoid arthritis, osteoporosis, Alzheimer's disease, multiple sclerosis, and other autoimmune and degenerative diseases (Pershadsingh, *Expert Opin. Investig. Drugs* 8:1859-1872 (1999); Neve et al., *Biochem. Pharmacol.* 60:1245-1250 (2000); McGeer et al., *J. Neural. Transm. Suppl.* 59:53-7 (2000); Bar-Or et al., *J. Neuroimmunol.* 100:252-9 (1999); Papadakis and Targan, *Annu. Rev. Med.* 51:289-98(2000)). Pharmacological co-activation of both subtypes provides for a synergistic therapeutic effect. An essential aspect of this invention is a unique and novel approach to the treatment of such diseases that involves the unexpected outcome, that simultaneous pharmacological activation of both PPARalpha and PPARgamma leads to superior efficacy, compared to the effects derived from the algebraic sum of the effects of activation of PPARalpha or PPARgamma, independently. Synergy may be achieved either with a ligand that co-activates both PPARalpha and PPARgamma subtypes, or therapeutic compositions consisting of a PPARalpha agonist and a PPARgamma agonist resulting in attenuating, arresting, reversing or preventing the target disease.

[0051] This aspect of the invention is illustrated in the unique approach to the treatment of atherosclerosis or psoriasis, that have dermatological or vascular manifestations of a chronic disease with inflammatory, proliferative and degenerative (apoptotic) components. The pathogenesis of both atherosclerosis and psoriasis involve inappropriate proliferation (vascular smooth muscle cells in atherosclerosis and epidermal keratinocytes in psoriasis) and expression of inflammatory cytokines, mediated

by activation of the inflammatory transcription factors, NF-kappaB, AP-1 and NFAT (Neve et al., *Biochem. Pharmacol.*, 60:1245-1250 (2000) and Ellis et al., *Arch. Dermatol.* 136:609-16(2000)). Specific activation of PPARgamma on the one hand (Ellis et al., *Arch. Dermatol.* 136:609-16(2000)), and specific activation of PPARalpha on the other (Kornuves et al., *J. Invest. Dermatol.* 115:353-60(2000)) have been shown to independently stimulate keratinocyte differentiation and inhibit and epidermal proliferation. Similarly, for example, activation of PPARgamma inhibits proliferation of vascular smooth muscle (VSM)cells, and iNOS production and matrix metalloproteinase (MMP) activity in the vessel wall, whereas activation of PPARalpha decreases the activity of cell adhesion moles and affects lipoprotein metabolism, resulting in a profound anti-dyslipidemic systemic effect (Neve et al., Biochem. Pharmacol. 2000; 60:1245-1250). Thus, unexpectedly, pharmacological co-activation of PPARalpha and PPARgamma can provide synergistic therapy in the treatment of atherosclerosis or psoriasis.

[0052] Via negative regulation of NF-kappaB and AP-1 signaling pathways, PPARalpha inhibits expression of inflammatory genes, such as interleukin-6, cyclooxygenase-2, endothelin-1, and the expression of monocyte-recruiting proteins such as vascular cell adhesion molecule (VCAM)-1, and recruitment of monocytes and foam cells in atherosclerotic lesions. Also via negative regulation of NF-kappaB and AP-1 signaling pathways, PPARgamma activation in macrophages and foam cells inhibits the expression of genes encoding iNOS, MMP-9, scavenger receptor A, VCAM-1. Therefore treatment modalities involving the simultaneous activation of PPARalpha and PPARgamma can provide a synergistic therapeutic effect and leading to superior improvement, resolution or prevention of systemic cardiovascular inflammation, including atherosclerosis, vascular restenosis, congestive heart failure and myocardial fibrosis (Takano et al., *Circ. Res.* 87:596-602(2000); Lee et al., *Circ. Res.*, 87:516-21 (2000); Fruchart et al., *Curr. Opin. Lipidol.* 10:245-57(1999)).

[0053] The compound may be a PPAR ligand with properties selected from the group consisting of: 1) a PPARgamma agonist, 2) a PPARgamma partial agonist (i.e. as

SPARM (slective PPAR modulator), 3) a PPARgamma antagonist, 4) a PPARalpha agonist, 5) a PPARalpha partial agonist, 6) a PPARalpha antagonist, 7) a PPARdelta agonist, 8) a PPARdelta partial agonist, 9) a PPARdelta antagonist, 10) a PPARgamma/PPARalpha dual agonist), 11) a PPARgamma/PPARdelta dual agonist, 12) a PPARalpha/PPARdelta dual agonist, 13) a PPARgamma partial agonist that also activates PPARalpha, 14) a PPARgamma partial agonist that also activates PPARdelta, and 15) a ligand that activates all three PPAR isoforms, a PPARgamma/PPARalpha/PPARdelta pan-agonist.

Methods for Design of Compounds

[0054] In some embodiments, the compounds disclosed herein may be designed by certain design methods as disclosed herein.

[0055] This invention relates to compounds that can act as ligands that bind and covalently modify nuclear receptors, with consequent activation or deactivation the particular nuclear receptor. In one aspect, the present invention relates to ligands capable of forming a covalent bond between the ligand and a cysteine residue in the nuclear receptor. Another aspect of this invention relates to geometric constraints on the ligand designed to provide for enhanced binding to nuclear receptors, in particular the peroxisome proliferator-activated receptors (PPARs). Another aspect of the present invention relates to methods of associating a particular disease or condition with a particular nuclear receptor. Another aspect of the present invention is the prevention or treatment of a disease associated with a nuclear receptor through ligand-induced activation or deactivation of a particular receptor.

[0056] The methods described in this invention relates to improvements in recruiting co-activators and/or co-repressors in order to optimize the activation or inactivation of the various PPAR isoforms in the treatment or prevention of a particular disease involving, for example: 1) promoting apoptosis of neoplastic cells, 2) inhibiting apoptosis in degenerative diseases such as multiple sclerosis and other autoimmune diseases, 3) inhibiting systemic inflammation by suppressing Th1-mediated inflammatory cytokines

and promoting Th1 to Th2 phenotypic transition, leading to treatment or prevention diseases such as atherosclerosis, syndrome X and congestive heart failure.

[0057] Other nuclear receptors to which the present invention applies are: the constitutive androstane (xenobiotic) receptor (CAR), the retinoid X receptor (RXR), the pregnane X receptor, the Farnesiod X receptor, the liver X receptor, and the steroid X receptor. These nuclear receptors contain cysteine residues in their ligand binding domains (LBDs), and in both the apo-LBD and the ligand-bound complex of these receptors contain the AF-2 helix motif which is essential for specific ligand binding and adopt a conformation similar to that of the PPARs, in particular PPARgamma.

[0058] In one aspect, this invention discloses compounds that bind to nuclear receptors by forming a disulfide linkage between a thiol group in the ligand and a cysteine residue in the receptor. In another aspect, the invention discloses compounds containing a halogen-substituted pyridine group that can form a covalent linkage with a cysteine residue in a particular nuclear receptor. Typically, the substituted pyridine group is located at the tail-end of the molecule.

[0059] In another aspect, this invention discloses compounds with molecular characteristics that enhances their binding affinity to the ligand-binding domain (LBD) of PPAR nuclear receptors, wherein the compound has structural features and constraints that enhance (optimize) receptor binding in order to maximize transactivation or deactivation. Preferred ligands contain a lipophilic headgroup that promotes high affinity binding to activating site of the of the PPAR LBD, leading to efficient PPAR transactivation, i.e. the binding of agonist ligands to the receptor resulting in changes in the expression level of mRNAs encoded by PPAR target genes. Receptor deactivation may occur when is covalently bound, but the headgroup fails to effectively engage the activating site of the LBD, resulting in failure of the ligand to transactivate the nuclear receptor.

[0060] The structure of the PPARgamma LBD has been determined by X-ray crystallography (Nolte et al., *Nature* 395:137-43(1998)). The PPARgamma LBD is a bundle of 13 alpha-helices and a small four-stranded beta-sheet (Willson et al. *J. Med.*

Chem. 43:527-50(2000)), with an overall fold similar to other nuclear receptor structures from helix 3 to the C-terminus. The crystal structure of the apo-PPARgamma LBD revealed a large (~1300 $Å^3$) Y-shaped ligand-binding site located within the bottom half of the LBD. The PPARgamma thiazolidinedione (TZD) agonist, rosiglitazone binds in a U-shaped conformation, while occupying only 40% of the ligand-binding site. The TZD headgroup makes several specific hydrogen-bonding interactions with His449, Tyr473, His323, Ser289, and Gln286 (Willson et al., *J Med Chem.* 2000;43:527-50). Tyr473 lies on the C-terminal AF-2 helix, which is critical for transcriptional activation. This interaction of the ligand with the AF-2 helix locks the receptor in an activated state.

[0061] Similarly, PPARdelta and, based on theoretical considerations, PPARalpha both have large (~1300 $Å^3$) Y-shaped ligand-binding sites located within the bottom half of the LBD, requiring hydrogen bond interaction with Tyr 473 for transcriptional activation. In contrast, an inactivating ligand is one which binds with high affinity to the PPAR LBD without hydrogen-bonding interactions with Tyr 473, and failure to transactivate the transcriptional machinery. In this latter case, a specific inactivating compound that also covalently binds to a cysteine residue in the receptor, can non-competitively and irreversibly block receptor activation. In both the apo and ligand-bound structures of PPARgamma, the AF-2 helix adopts a conformation similar to other ligand-bound nuclear receptors (Weatherman et al., 1999;68, 559-581).

[0062] In another aspect, the present invention discloses methods for activating or deactivating a nuclear receptor by covalently linking a ligand to the LBD. One method disclosed herein is the strategic incorporation a thiol group in the ligand such that it is capable of forming a disulfide bridge with the sulfhydryl group of a cysteine residue in the nuclear receptor LBD. A second method disclosed herein is the strategic incorporation of a halogenated pyridyl group at the tail-end terminus of the ligand such the pyridine ring is capable of forming a covalent bond with the sulfhydryl group of a cysteine residue in the nuclear receptor LBD.

[0063] In another aspect the present invention discloses methods that provide for optimal binding to the PPAR LBD, and relates to specific geometric constraints on the

ligand. These constraints consist of angular torsion, i.e. a bend, in the ligand at an optimal distance from the head group. As discussed above, the PPAR LBD contains an overall fold similar to other nuclear receptor structures from helix 3 to the C-terminus. The conformation of the PPAR LBD is such that a ligand must clear the helix-3 fold in order to fit within the LBD. Geometrically, this requires a twist or torsional bend in the ligand molecule, and can be accomplished by inserting a chemical group capable of inducing required angular flexion in the molecule.

[0064] The torsional angle is measured by examining computer models of rosiglitozone in PPARgamma, a selective thiazolidinedione derivative that has a low EC50 for PPARgamma transactivation (< 1 nM, as measured by FRET analysis) (*see* U.S. Pat. No: 6,127,394). Based on structural considerations, the intra-ligand torsion angle is optimally 45 to 85 degrees with a torsion angle of 60 to 70 degrees preferred. Examples of preferred chemical groups capable of inducing the required intra-molecular torsion are one or more of the following: cis-C=C-, cis-C=C-C=C-, -C=O (carbonyl), -CONH- (amide), substituted or unsubstituted phenyl, substituted or unsubstituted cis-cyclopropyl.

[0065] Also based on molecular modeling and structural considerations, the lower limit of the distance (d_1) between the headgroup of the ligand and the apex of the torsion angle is optionally 3.5 Angstroms, with 4.0 Angstroms preferred. In one embodiment, ligands include chemical substituents that can effect formation of a covalent bond with a cysteine in the ligand binding domain.

[0066] In another aspect, the present invention relates to methods of associating a particular disease or condition with a particular nuclear receptor, for example, the nuclear receptor PPARgamma. By associating, is meant that a particular disease or condition can be treated by administration of a compound of this invention that activates or deactivates the particular nuclear receptor. As used herein, and as well-understood in the art, "treatment" is an approach for obtaining beneficial or desired results, including clinical results. For purposes of this invention, beneficial or desired clinical results include, but are not limited to, alleviation or amelioration of one or more symptoms, diminishment of

extent of disease, stabilized (i.e., not worsening) state of disease, preventing spread of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable.

[0067] In another aspect, the present invention provides for a method of treating a nuclear receptor-mediated disease or condition by administration of a compound of this invention that activates or deactivates the particular nuclear receptor by covalently modifying the nuclear receptor through formation of a covalent bond between the sulfhydryl group or the substituted pyridine of the ligand and a cysteine residue in the nuclear receptor. Preferred compounds of this invention are capable of binding to the LBD of a particular nuclear receptor and forming a covalent bond with a cysteine residue therein.

[0068] A library of compounds having formulae described herein can be prepared. The binding affinity of a compound of this invention to a particular receptor can be determined using well-described binding assays. The ability of a compound of this invention to activate a particular receptor can also be determined using well-described transcriptional activation assays.

[0069] In one embodiment, a method for designing a compound that is an L-shaped ligand molecule capable of binding to at least one of PPAR-α, δ, and γ, is provided. In one embodiment, the method includes:

identifying at least one ligand binding domain (LBD) in a selected PPAR;

selecting at least a first chemical group capable of binding to the LBD of the PPAR;

selecting a second chemical group capable of interacting with at least one amino acid in the LBD to have an effect on transcription mediated by the PPAR; and

determining a formula of an L-shaped ligand molecule wherein the L-shaped ligand molecule comprises a first leg section and a second leg section, the first leg section comprising the first chemical group that binds the LBD of the PPAR, and the second leg section comprising the second chemical group which interacts with an amino acid on the PPAR, and further wherein the first and second leg sections of the L-shaped ligand

molecule are connected at an elbow atom common to both legs such that the first and second legs are capable of orienting in a conformation which creates an angle of about 80 to 110 degrees between the first and second legs.

[0070] Optionally, the method can also include synthesizing the L-shaped ligand molecule and determining its ability to bind to at least one of PPAR-α, δ, and γ.

[0071] The LBD of the PPAR may comprise a cysteine residue. The first chemical group may comprise a thiol which is capable of forming a disulfide linkage with the cysteine residue in the LBD. The first leg section of the L-shaped ligand molecule may comprise a lipophilic terminal group that promotes binding to an active site of a PPAR isoform. The first chemical group may comprise a halogen-substituted pyridine group which which is capable of forming a covalent linkage with the cysteine residue in the LBD.

[0072] Interaction of the amino acid of the LBD with a second chemical group on the L-shaped ligand molecule may be via hydrogen bonding. The compound may be an activating ligand that binds the PPAR, and a second chemical group on the L-shaped ligand molecule may interact with a Tyr473 residue on the PPAR.

[0073] The L-shaped ligand molecule may be an inactivating ligand that binds the PPAR, wherein the second chemical group on the L-shaped ligand molecule does not interact with a Tyr473 residue on the PPAR. Further, an L-shaped ligand molecule may be designed for optimal binding to a PPAR LBD by determining at least one geometric constraint on the ligand. Optionally, the L-shaped ligand molecule is an agonist of the PPAR or an antagonist of the PPAR.

[0074] In another embodiment, a computer-assisted method for designing an L-shaped ligand molecule specific for at least one of PPAR-α, δ, and γ, using a programmable computer including a processor, an input device, and an output device is provided. The method comprises in one embodiment:

(a) inputting into the programmable computer, through the input device, data including the identity of at least one ligand binding domain (LBD) in the selected PPAR;

(b) determining, using the processor, the identity of at least a first chemical

group capable of binding to the LBD of the PPAR;

(c) determining, using the processor, the identity of a second chemical group capable of interacting with at least one amino acid in the LBD to have an effect on transcription mediated by the PPAR; and

(d) outputting, to the output device, the formula of an L-shaped ligand molecule wherein the L-shaped ligand molecule comprises a first leg section comprising the first chemical group which binds the LBD of the PPAR, and a second leg section comprising the second chemical group which interacts with an amino acid on a PPAR, and further wherein the first and second leg sections of the ligand molecule are connected at an elbow atom common to both leg sections, such that the first and second leg sections are capable of orienting in a conformation with an angle of about 80 to 110 degrees with respect to each other. The L-shaped ligand molecule may be designed for optimal binding to a PPAR LBD by determining at least one geometric constraint on the molecule.

[0075] Another method for designing an L-shaped ligand molecule capable of binding to at least one of PPAR-α, δ, γ is provided. The method comprises identifying an L-shaped molecule comprising a first leg section L_1 and a second leg section L_2 wherein the longitudinal axes of L_1 and L_2 are connected by a shared elbow atom c, wherein:

(a) L_1 and L_2 are capable of assuming approximately linear extended conformations wherein L_1 and L_2 are independently each about 9-13 Å in length;

(b) leg sections L_1 and L_2 are connected at the elbow atom c such that the first and second leg sections are capable of orienting in a conformation which creates an angle of about 80 to 110 degrees between the first and second legs;

(c) a terminus of L_1 contains an acidic moiety of pK_a between 4 and 6, and has acceptor atoms capable of hydrogen-bonding; and

(d) a terminus of L_2 contains a moiety selected from the group consisting of a basic moiety, an acidic moiety, functional groups of varying polarity, and a neutral hydrocarbon moiety. Optionally, the angle between leg sections L_1 and L_2 is about 90 degrees.

[0076] The L-shaped ligand molecules identified by the method described herein are optionally synthesized, and optionally tested for an ability to bind at least one of PPAR-α, δ, and γ or PPAR isoforms. Optionally, L_1 and L_2 independently are about 11-12 Å. Optionally, L_1 is about 11.1 Å and L_2 is about 11.4Å.

[0077] Optionally, an L-shaped ligand molecule is designed that is capable of assuming a configuration wherein a torsional dihedral angle is generated by atoms a-b-c-d of the molecule, wherein atoms a and b are adjacent connected atoms in leg section L_1, atom b is connected to elbow atom c, and atom c is connected to atom d in leg section L_2, further wherein:

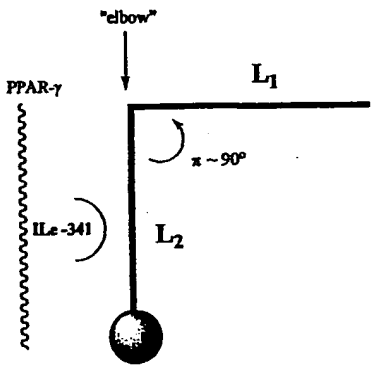
a dihedral angle between a plane containing the atoms a, b and c and a plane containing the atoms b, c and d is between 45 and 85 degrees; and

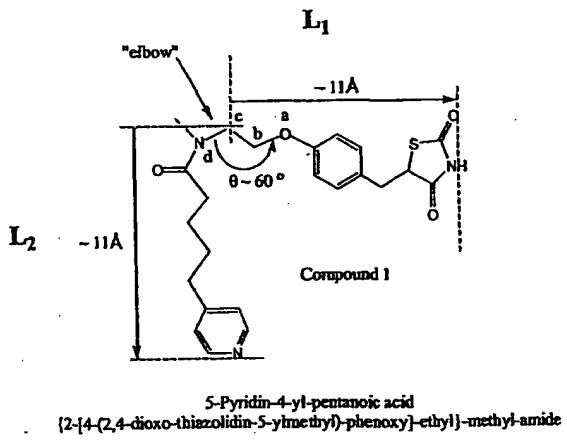
a distance from an L_1 head group acid proton to an apex of the dihedral angle is at least about 3.5Å.

[0078] In one embodiment, the invention relates to L-shaped molecules designed by the method discussed in the preceeding section that are ligands for PPAR-α, δ, or γ or any combination of isoforms wherein each leg, L_1 and L_2 (as shown, for example, in Schemes 1a and 2a), of the L-shaped molecule is of approximately the same length, about 9-13 Å, preferably 11-12 Å, and optimally L_1 is 11.1 Å and L_2 is 11.4 Å respectively. In one embodiment, L_1 and L_2 comprise chemical moieties that are in approximately linear extended conformations, and L_1 and L_2 are connected at an elbow atom c such that L_1 and L_2 can adopt an L shape. The first non-H atom at which one side chain L_1 deviates significantly from a straight line and traverses in an approximately 90° angle e.g., 80-110° down L_2 is c, and the angle between chains is called pi, describing the elbow of this L (Scheme 1a). This angle pi is a geometric angle using the long axes of the L_1 and L_2 legs of L.

[0079] However, another measurement of use is the torsional angle theta generated by the elbow atom c, and atom d of L_2 adjacent to atom c, and two adjacent atoms a and b of L_1 wherein atom a is also adjacent to elbow atom c, where the dihedral angle between the plane containing the atoms a, b and c and the plane containing the atoms b, c and d is

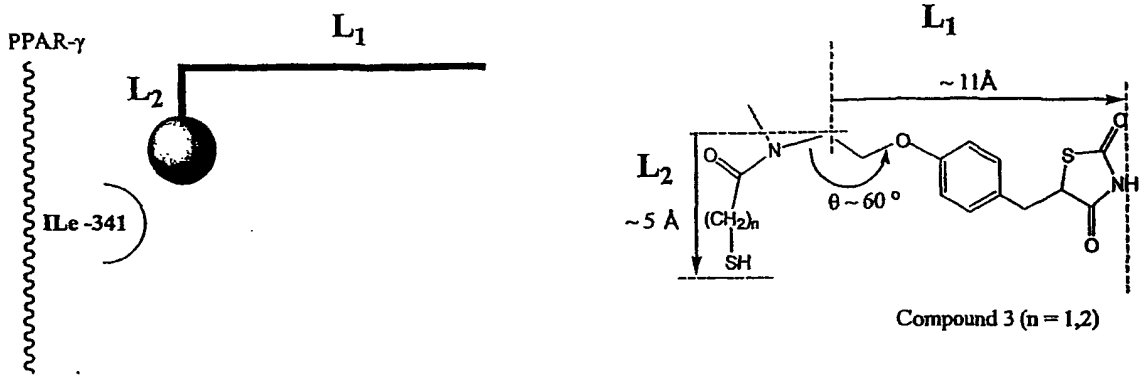
between 45 and 85 degrees, e.g. 60-70 degrees. An angle theta of 60° is optimal. An acceptable distance from the L_1 head group acid proton and the torsion angle apex is about 4 Å and a minimum distance of 3.5 Å . The terminus of L_1 in one embodiment contains an acidic moiety of pK_a approximately 4-6, and has acceptor atoms capable of hydrogen-bonding (e.g. S, N or O atoms). The terminus of L_2 can for example contain either a basic moiety ($pK_a \sim 7$-12), an acidic moiety ($pK_a \sim 4-6$), functional groups of varying polarity (variable pK_a), or a neutral hydrocarbon moiety (aryl, alkyl, alkenyl, alkynyl). L shaped compounds wherein the L_2 length is shortened by ~ 3 Å, can have poor activity as a result of the terminal ring making severe stereoelectronic interaction with Ile-341 in the PPAR-γ receptor (Figure 4). A larger ligand substituent in proximity to Ile-341 would clearly create a significantly unfavorable thermodynamic interaction.





5-Pyridin-4-yl-pentanoic acid
[2-[4-(2,4-dioxo-thiazolidin-5-ylmethyl)-phenoxy]-ethyl]-methyl-amide

Scheme 1a.



Compound 3 (n = 1,2)

Scheme 2a

[0080] In another embodiment the compounds are L shaped, wherein the L_2 length is shortened by 6-10 Å. These will have good activity as a result of the fact that the interaction with Ile-341 cannot occur (Scheme 2a).

[0081] In another embodiment of the compound, the terminal group for L_1 is the acid proton of a 2,5-thiazolidinedione which, together with the other heteroatoms of the TZD ring, makes contacts with His-449, His-323; Tyr-473; Ser-289; and Gln-286 forming a network of hydrogen bonds.

[0082] In another embodiment of the compound, the terminal group for L_1 is any acid group capable of donating and accepting H-bonds to this complex of His-449, His-323 and Tyr-473.

[0083] In another embodiment of the compound, the terminal group for L_2 is a pyridyl N of a 1,4-substituted pyridine.

[0084] In another embodiment of the compound, the terminal group for L_2 is a pyridyl N of a 1,3-substituted pyridine.

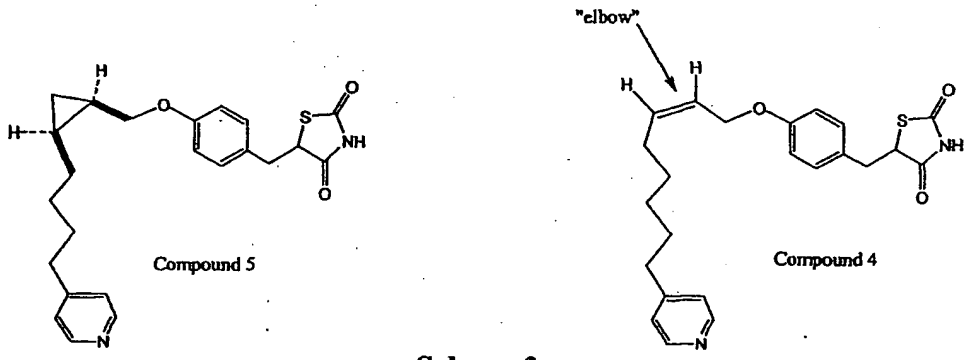
[0085] In another embodiment of the compound, the terminal group for L_2 is a pyridyl N of a 1,2-substituted pyridine.

[0086] In another embodiment of the compound, the terminal group for L_2 is any mono or bicyclic aromatic heterocycle.

[0087] In another embodiment of the compound, the terminal group for L_2 is any mono or bicyclic heterocycle, subject to size restrictions in the PPAR isoforms L_2 terminal pocket.

[0088] In another embodiment of the compound, the elbow atom c connecting L_1 and L_2 is contained within an N-methyl amide.

[0089] In another embodiment of the compound, the elbow atom c connecting L_1 and L_2 is contained within a cis-double bond (Scheme 3a).



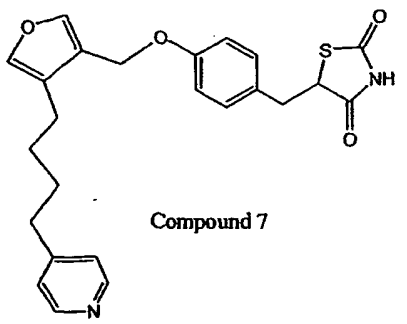
Scheme 3a

[0090] In another embodiment of the compound, the elbow atom c connecting L_1 and L_2 is contained within a cis-disubstituted cyclopropyl ring (Scheme 3a).

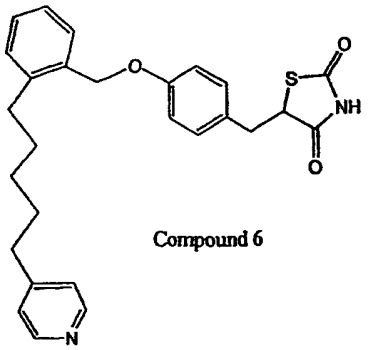
[0091] In another embodiment of the compound, the elbow atom c connecting L_1 and L_2 is contained within a ortho-disubstituted benzenoid or heterocycle (Scheme 4a).

[0092] In another embodiment of the compound, the elbow atom c connecting L_1 and L_2 is contained within a meta-disubstituted benzenoid or heterocycle.

[0093] In another embodiment of the compound, the elbow atom c connecting L_1 and L_2 is contained within a para-disubstituted benzenoid or heterocycle such as ortho-disubstituted benzenoid (6) or heterocycle (furanoid, 7) as shown below .



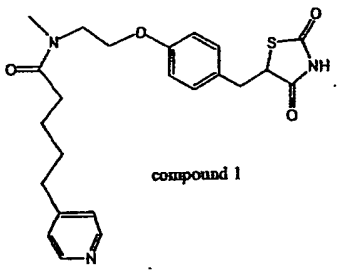
Compound 7



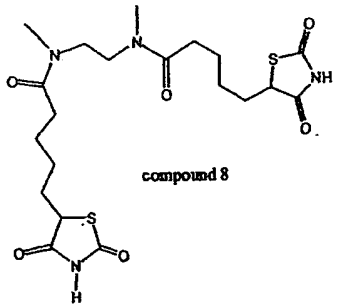
Compound 6

Scheme 4a

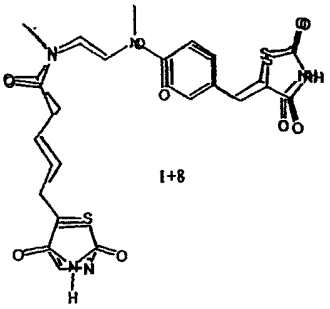
[0094] In another embodiment of the compound, both L_1 and L_2 are identical, as shown below in Scheme 5a:



compound 1



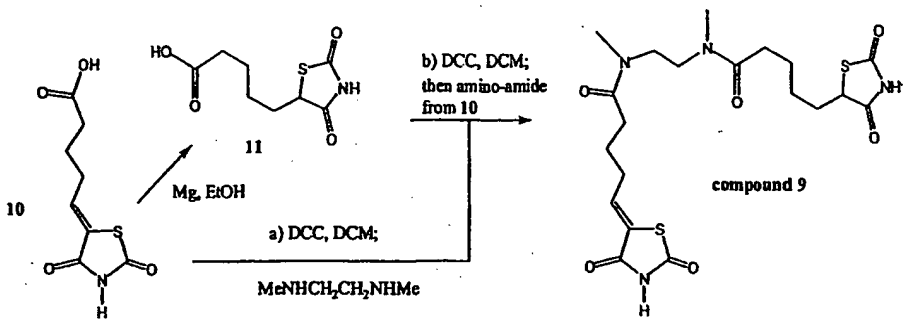
compound 8



1+8

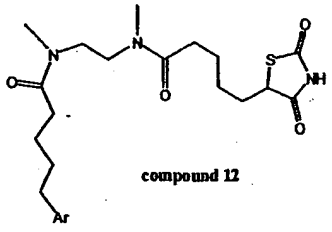
Scheme 5a

[0095] In another embodiment of the compound, L_1 and L_2 are closely similar, using an intermediate for L_1 **10** as L_2 **11**, i.e. compound **9** in Scheme 6a. Synthesis of L_1 **(11)** for compound **8** is accomplished by reduction of compound **10**. Coupling of **10** and **11** gives compound **9**, a dehydro-analogue of compound **8.**



Scheme 6a.

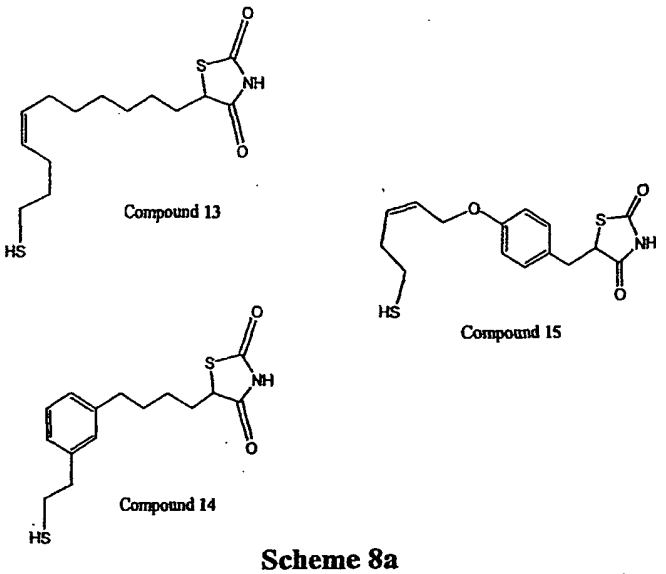
[0096] In another embodiment of the compound, the L_2 TZD ring is replaced with a heterocyclic ring (Ar) such as a 2, 3 or 4 pyridyl ring. (Scheme 7a).



e.g., Ar = 2, 3 or 4 pyridyl ring

Scheme 7a

[0097] In another embodiment of the compound, the terminal group for L_2 is a sulfhydryl SH, with either one or two methylene atoms separating the SH from the amide carbonyl, for example compound 3 in Scheme 2a. The SH of compound 3 may form a covalent disulfide bridge to PPARγ. Some examples such as Cis-olefin or meta-aromatic elbows connecting sulfhydryl terminated L_2 domain to the L_1 domain, are shown in Scheme 8a.



Scheme 8a

[0098] In another embodiment of the compound, there are no aromatic rings and they resemble natural ligands, such as compound **13**, i.e. 5-(11-Mercapto-undec-7-enyl)-thiazolidine-2,4-dione.

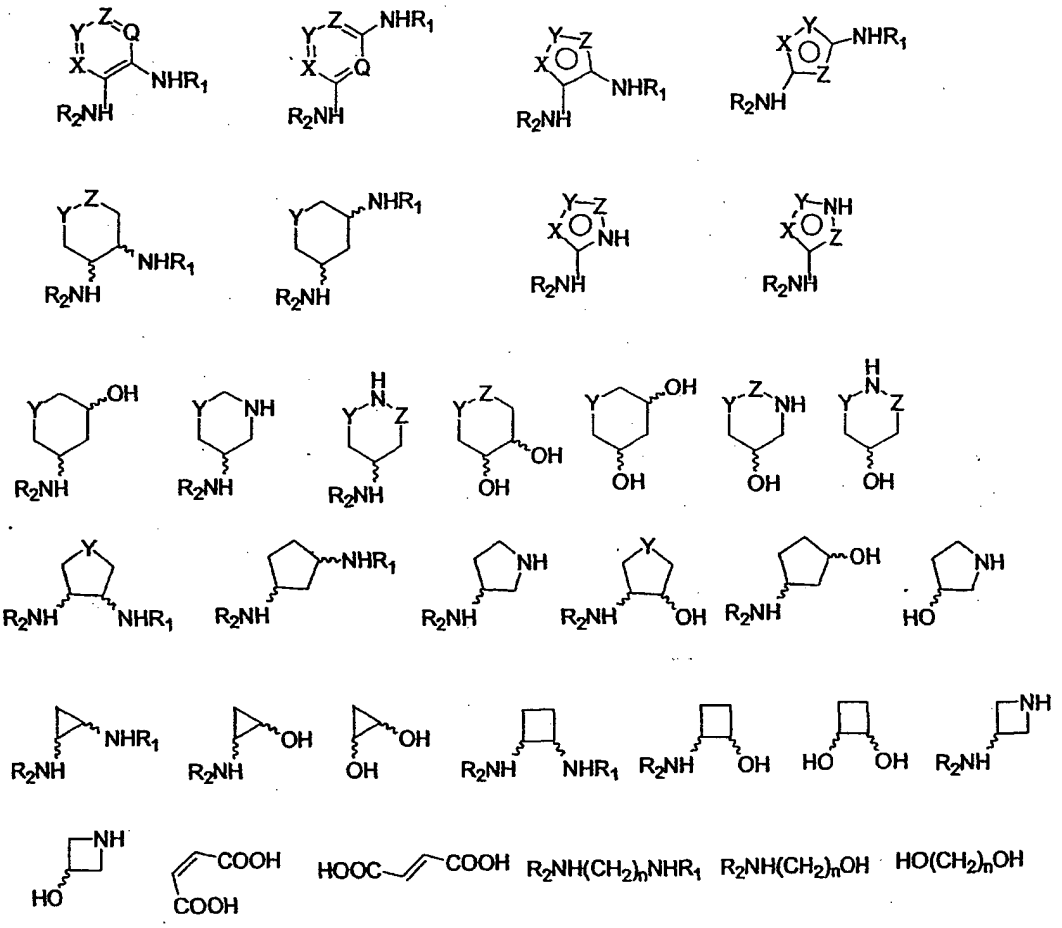
[0099] In another embodiment of the compound, there is only one central elbow aromatic ring and otherwise resemble natural ligands, such as compound **14**.

[0100] In another embodiment of the compound, the terminal SH is converted to a prodrug for oral bioavailability (oral administration), and to promote formulation stability. Examples include thioesters, thiocarbonates, thiourethanes, thioethers, and others.

[0101] In another embodiment of the compound, the aforementioned elbow moiety, whose centroid is for example, approximately equidistant from the termini of either L_1 or L_2, is chosen from the group of scaffolds shown in Scheme 9a . Each L_1 and L_2 group may be connected to the scaffolds via free NH or OH groups. For the 6-membered aromatic scaffolds, the groups X, Y, Z, Q can be optionally selected from N, CH, CR, C-OH, C-Ar, C-NR_3R_4, C-halogen, and so on. For the 5-membered aromatic rings, X, Y and Z are selected optionally from CH, CR, CAr, COH, C-halogen, NH, N, NR, S, O and

so on. For the nonaromatic rings, only Y and Z are selected optionally from CH2, CHR, CR_3R_4, CHAr, CHOH, CH-halogen, NH, S, O, and may contain unsatuations in differing locations. For acyclic scaffolds, diamines, aminoalcohols, diols, diacids and the like of varying chain length with n = 2 being preferred are also shown in Scheme 9a.

[0102]



Scheme 9a.

[0103] In one embodiment, the compounds shown in Figure 5 are provided wherein:

X is H, halogen, $-CH_3$, $-OCH_3$, $-NH_2$, or $-NO_2$;

Y is H, halogen, $-CH_3$, $-OCH_3$, $-NH_2$, or $-NO_2$;

n is C_{1-6} alkyl;

R_1 is H, C_{1-6} alkyl, or phenyl optionally substituted with 1 or 2 groups selected fromC_{1-3} alkoxy, and halogen. Preferred compounds of this invention are capable of binding to the ligand binding domain of a nuclear receptor and forming a covalent bond with a cysteine residue of the receptor;

preferably R_1 is $-CH_3$; and

R_2 is a hydrophobic organic group with molecular weight less than 500 Daltons;

preferably, X and Y are independently Cl, F or Br, most preferably, X is Cl;

or R_2 is C_{1-3} alkenyl-adamantyl;

R_3 is H, mono-substituted or unsubstituted phenyl, or C_{1-3} alkyl, oxygen, or a direct link;

most preferably R_3 is oxygen.

[0104] Preferred compounds are capable of binding to the LBD of a nuclear receptor and forming a covalent bond with a cysteine residue of the receptor. Preferred compounds with a suitable apparent pKi (for inhibition or deactivation) or pKa (for activation), where pKi > 5, preferably > 7 for deactivation; and pKa > 5, preferably > 7 for activation.

[0105] The present invention provides a method for the treatment of a nuclear receptor-mediated disease or condition by administration of a compound that activates or deactivates the particular receptor that is associated with said disease or condition, using the methods described in this invention.

[0106] With reference to structure 3 in Figure 6, for a ligand to bind to the PPARgamma LBD and activate transcription, the ligand requires a head group with

capability of forming H-bond interaction with His449, His323, and Tyr473 in the AF-2 helix. Ideally, the head group should be 2.5A from a central aromatic ring (distance between 1 and 2), which occupies a narrow pocket between Cys285 and Met364. The aromatic ring resides over the helix-3. The oxygen atom (3) and the amide functionality (4) provide a vital geometry to the tail (lipoate group) through the carbon linkers with a torsion angle of 64.3 degrees, as shown above.

[0107] The distances and the angles are determined by molecular modeling by methods familiar to those skilled in the art. The PPAR structure and ligands can be downloaded from the Proteinn Data Bank on the World Wide Web. H.M. Berman, J. Westbrook, Z. Feng, G. Gilliland, T.N. Bhat, H. Weissig, I.N. Shindyalov, P.E. Bourne:The Protein Data Bank, *Nucleic Acids Research*, **28** pp. 235-242 (2000).

[0108] The PPAR structure and ligands can be visualized using commercially available software such as Swiss-PdbViewer (GlaxoSmithKline, Geneva, Switzerland) or RasMol (Biomolecular Structures Group, Glaxo Wellcome Research & Development Stevenage, Hertfordshire, UK) (e.g., WinRas/WinTop) on for example a PC platform.

[0109] Structure 1 in Figure 6 represents a case where a benzene ring could provide the desired bend, i.e. the required torsional constraint in the molecule by virtue of the substitution (meta) pattern. The benzene ring is shown between the carbons numbered 3 and 5.

[0110] Structure 2 in Figure 6 represents a similar case, but the benzene ring is now located between the carbons numbered 5 and 7. The required torsional constraint or bend in the molecule is conferred by virtue of the substitution (meta) pattern. Thus, position of the bend in the molecule can be altered by strategic placement a benzene ring. The benzene ring is optionally substituted in any unoccupied position; wherein the substituent group is selected from the group consisting of one or more of the following: hydrogen, hydroxy, methyl, halogen, methoxy, ethoxy, alkyl, aryl, and arylalkyl.

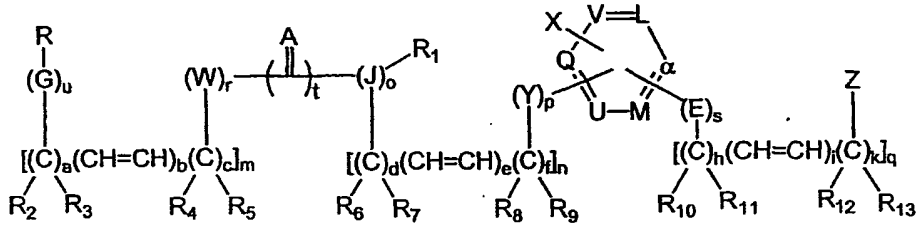
[0111] The torsional constraints shown in the examples above allows the ligand to traverse helix 3 thereby providing a better and tighter fit within the LBD of the receptor.

According to the present invention, these compounds would have a higher affinity for the particular PPAR receptor.

Compounds According to the Invention

[0112] Exemplary compounds capable of interacting with PPAR receptors include the following:

Case 1 represents compounds of the formula:



wherein the following apply:

a = 0-8; **c** = 0-8; **d** = 0-8; **f** = 0-8; **h** = 0-8; **k** = 0-8.

b = 0-4; **e** = 0-4; **i** = 0-4 (when **b**, **e** or **i** are =1, double bonds are either *E* or *Z*; when **b**, **e** or **i** are >1, any mixture of *E* or *Z* diastereomers is possible).

m = 0-4; **n** = 0-4; **q** = 0-4.

u = 0, 1; **r** = 0, 1; **p** = 0, 1; **s** = 0, 1; **t** = 0, 1; **o** = 0, 1.

R = cycloalkyl, heterocycloalkyl, alkyl, aryl, heteroaryl, R_6NH, R_6R_7N, R_8S, R_8SO, R_8SO_2, R_8SO_2NH, $R_8SO_2NR_9$, $R_{10}CO$, $R_{10}OCO$, $R_{10}NHCO$, $R_{10}R_{11}NCO$, $R_{12}O$, $R_{13}SCO$, $R_{14}NCONHR_{15}$, R_8NSO_2NH, $R_8NSO_2NR_9$, $R_{10}NCO$, $R_{10}OCONR_{16}$, $R_{10}NHCO$, $R_{10}R_{11}NCO$, $R_{13}SCONR_{17}$.

A = O, S.

$\mathbf{R^1} - \mathbf{R^{13}}$ = independently H, optionally substituted alkyl, cycloalkyl, alkylcycloalkyl, arylalkyl, aryl, heteroaryl, heterocyclic, alkylheteroaryl, alkylheterocyclic.

W = O, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, $-SO_2-$, -SONH-, -NHSO-, $-NR^1SO-$, $-SONR^1-$, $-SO_2NH-$, $-NHSO_2-$, $-NR^1SO_2-$; $-SO_2NR^1-$, $-SO_3-$ (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; $-ONR^1$; NR^1O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-;

G = O, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, $-SO_2-$, -SONH-, -NHSO-, $-NR^1SO-$, $-SONR^1-$, $-SO_2NH-$, $-NHSO_2-$, $-NR^1SO_2-$; $-SO_2NR^1-$, $-SO_3-$ (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; $-ONR^1$; NR^1O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-;

E = O, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, $-SO_2-$, -SONH-, -NHSO-, $-NR^1SO-$, $-SONR^1-$, $-SO_2NH-$, $-NHSO_2-$, $-NR^1SO_2-$; $-SO_2NR^1-$, $-SO_3-$ (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; $-ONR^1$; NR^1O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-;

J = O, NH, NR^1 (e.g. N-Me), S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, $-SO_2-$, -SONH-, -NHSO-, $-NR^1SO-$, $-SONR^1-$, $-SO_2NH-$, $-NHSO_2-$, $-NR^1SO_2-$; $-SO_2NR^1-$, $-SO_3-$ (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; $-ONR^1$; NR^1O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-.

X = H, halogen, OR^1, O, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, $-SO_2-$, -SONH-, -NHSO-, $-NR^1SO-$, $-SONR^1-$, $-SO_2NH-$, $-NHSO_2-$, $-NR^1SO_2-$; $-SO_2NR^1-$, $-SO_3-$ (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; $-ONR^1$; NR^1O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-, with X attached either *meta* or *para*.

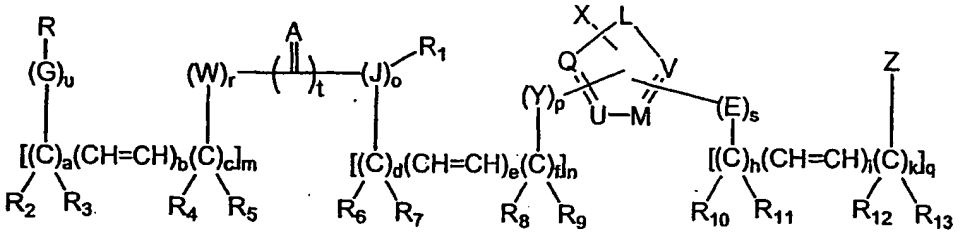
Y = H, O, OR^1, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)=O-, $-SO_2-$, -SONH-, -NHSO-, $-NR^1SO-$, $-SONR^1-$, $-SO_2NH-$, $-NHSO_2-$, $-NR^1SO_2-$; $-SO_2NR^1-$, $-SO_3-$ (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; $-ONR^1$; NR^1O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-, with Y attached either *meta* or *para*.

Q,L,M, V, α, and **U** are any combination of **Q** = CH, N, N-oxide; **L** = CH, N, N-oxide; **M** = CH, N, N-oxide, **V** = CH, N, N-oxide, α = CH, N, N-oxide, and **U** = CH, N and N-oxide; where the point of attachment of Y

and X are usually via carbon atoms in the central ring. When X = OH and L = N, a 2- or 4-pyridinol is indicated, which automatically includes the keto-tautomers, the 2- and 4- pyridones. The side chain (Y_p) can be attached via the pyridone N, or at one of the remaining positions. Also, the ring can be benzenoid, pyridinoid, pyrimidinoid, and so on where benzenoid is preferred.

Z = CO_2R^1; *R* or *S* or racemic 5-substituted-thiazolidine-2,4-dione; *R* or *S* or racemic 3-substituted-pyrrolidine-2,5-dione; all diastereomers of 3,4-disubstituted-pyrrolidine-2,5-dione; *R* or *S* or racemic 4-substituted-azetidine-2-one; *R* or *S* or racemic 3-substituted-azetidine-2-one; all diastereomers of 3,4-disubstituted-azetidine-2-one; 3-substituted-azetidine-2,4-dione; 1-substituted-1,3-diazetidine-2,4-dione; 1-substituted-1,3-diazetidine-2-one; all diastereomers of 1,4-disubstituted-1,3-diazetidine-2-one; 5-substituted-2,4-dihydro-[1,2,4]triazol-3-one; 4-hydroxy-5-substituted-1,2-dihydro-pyrazol-3-one; 4-alkoxy-5-substituted-1,2-dihydro-pyrazol-3-one; 4-alkoxy-substituted-1,2-dihydro-pyrazol-3-one; 5-substituted-2H-pyrazole-3,4-dione; 5-substituted-imidazole-2,4-dione; 3-substituted-pyrrole-2,5-dione; 3-Hydroxy-4-substituted-pyrrole-2,5-dione; 3-alkoxy-4-substituted-pyrrole-2,5-dione; 3-alkoxy-substituted-pyrrole-2,5-dione; 5-substituted-oxazolidine-2,4-dione; 5-substituted-imidazolidine-2,4-dione; 5-substituted-1,2-dihydro-pyrazol-3-one; 5-substituted-2H-tetrazole; 4-substituted-2H-[1,2,3]triazole; 3-substituted-1H-[1,2,4]triazole; R or S or racemic 5-substituted-3,5-dihydro-[1,2,3]triazol-4-one; 5-substituted-2,3-dihydro-[1,2,3]triazol-4-one; R or S or racemic 4-substituted-pyrazolidine-3,5-dione; 4-substituted-[1,2,4]triazolidine-3,5-dione. Also, all benzo-fused examples of the above monocycles such as, but not limited to: 2, 3, 4 or 5-substituted-isoindole-1,3-dione; 3, 4 or 5-substituted-1,2-dihydro-indazol-3-one; 3, 4 or 5-substituted-2H-benzotriazole, and so on.

[0113] Case 2 represents compounds of the formula:



wherein the following apply:

a = 0-8; **c** = 0-8; **d** = 0-8; **f** = 0-8; **h** = 0-8; **k** = 0-8.

b = 0-4; **e** = 0-4; **i** = 0-4 (when **b**, **e** or **i** are =1, double bonds are either *E* or *Z*; when **b**, **e** or **i** are >1, any mixture of *E* or *Z* diastereomers is possible).

m = 0-4; **n** = 0-4; **q** = 0-4.

u = 0, 1; **r** = 0, 1; **p** = 0, 1; **s** = 0, 1; **t** = 0, 1; **o** = 0, 1.

R = cycloalkyl, heterocycloalkyl, alkyl, aryl, heteroaryl, R_6NH, R_6R_7N, R_8S, R_8SO, R_8SO_2, R_8SO_2NH, $R_8SO_2NR_9$, $R_{10}CO$, $R_{10}OCO$, $R_{10}NHCO$, $R_{10}R_{11}NCO$, $R_{12}O$, $R_{13}SCO$, $R_{14}NCONHR_{15}$, R_8NSO_2NH, $R_8NSO_2NR_9$, $R_{10}NCO$, $R_{10}OCONR_{16}$, $R_{10}NHCO$, $R_{10}R_{11}NCO$, $R_{13}SCONR_{17}$.

A = O, S.

$\mathbf{R^1} - \mathbf{R^{13}}$ = independently H, optionally substituted alkyl, cycloalkyl, alkylcycloalkyl, arylalkyl, aryl, heteroaryl, heterocyclic, alkylheteroaryl, alkylheterocyclic.

W = O, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, $-SO_2-$, -SONH-, -NHSO-, $-NR^1SO-$, $-SONR^1-$, $-SO_2NH-$, $-NHSO_2-$, $-NR^1SO_2-$; $-SO_2NR^1-$, $-SO_3-$ (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; -ONR^1; NR^1O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-; **G** = O, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, $-SO_2-$, -SONH-, -NHSO-, $-NR^1SO-$, $-SONR^1-$, $-SO_2NH-$, $-NHSO_2-$, $-NR^1SO_2-$; $-SO_2NR^1-$, $-SO_3-$

(sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; -ONR^1; NR^{1}O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-; **E** = O, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, -SO_2-, -SONH-, -NHSO-, -NR^{1}SO-, -SONR^1-, -SO_2NH-, -NHSO_2-, -NR^{1}SO_2-; -SO_2NR^1-, -SO_3- (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; -ONR^1; NR^{1}O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-; **J** = O, NH, NR^1 (e.g. N-Me), S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, -SO_2-, -SONH-, -NHSO-, -NR^{1}SO-, -SONR^1-, -SO_2NH-, -NHSO_2-, -NR^{1}SO_2-; -SO_2NR^1-, -SO_3- (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; -ONR^1; NR^{1}O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-.

X = H, halogen, OR^1, O, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, -SO_2-, -SONH-, -NHSO-, -NR^{1}SO-, -SONR^1-, -SO_2NH-, -NHSO_2-, -NR^{1}SO_2-; -SO_2NR^1-, -SO_3- (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; -ONR^1; NR^{1}O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-, with X attached either *meta* or *para*.

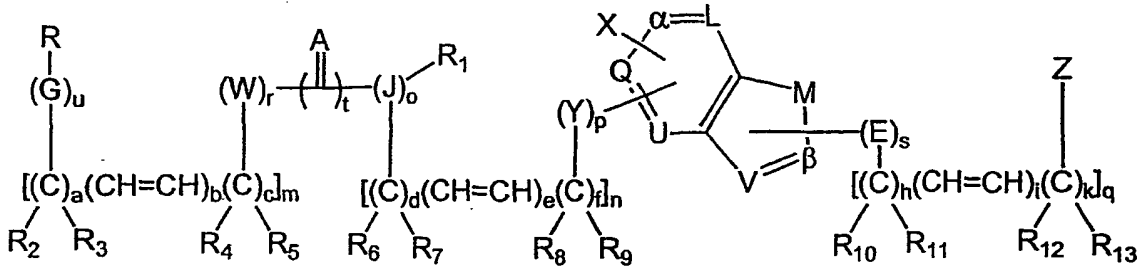
Y = H, O, OR^1, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)=O-, -SO_2-, -SONH-, -NHSO-, -NR^{1}SO-, -SONR^1-, -SO_2NH-, -NHSO_2-, -NR^{1}SO_2-; -SO_2NR^1-, -SO_3- (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; -ONR^1; NR^{1}O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-., with Y attached either *meta* or *para*.

Q,L,M,V and **U** are any combination of **Q** = CH, N, N-oxide; **L** = C=O, O, S, -:SO-, SO_2, N, NR, NH, N-oxide; **M** = CH, N, N-oxide, **U** = CH, N and N-oxide; and **V** = CH, N and N-oxide; where the point of attachment of Y and X are usually, but not necessarily, via carbon atoms in the central ring. When X = OH and L = N, a 2- or 3-pyrrolinol is indicated, which automatically includes the keto-tautomers, the 1,5-dihydropyrrol-2-one and 1,2-dihydropyrrol-3-one. The side chain (Y_p) can be attached via the pyrrolone N, or at one of the remaining positions. Also, the ring can contain multiple heteroatoms such as would be the case for: thiazoles,

isothiazoles, oxazoles, isoxazoles, histidines, pyrrazoles, triazoles, tetrazoles, and so on, where thiazole or isothiazole is preferred.

Z = CO_2R^1; *R* or *S* or racemic 5-substituted-thiazolidine-2,4-dione; *R* or *S* or racemic 3-substituted-pyrrolidine-2,5-dione; all diastereomers of 3,4-disubstituted-pyrrolidine-2,5-dione; *R* or *S* or racemic 4-substituted-azetidine-2-one; *R* or *S* or racemic 3-substituted-azetidine-2-one; all diastereomers of 3,4-disubstituted-azetidine-2-one; 3-substituted-azetidine-2,4-dione; 1-substituted-1,3-diazetidine-2,4-dione; 1-substituted-1,3-diazetidine-2-one; all diastereomers of 1,4-disubstituted-1,3-diazetidine-2-one; 5-substituted-2,4-dihydro-[1,2,4]triazol-3-one; 4-hydroxy-5-substituted-1,2-dihydro-pyrazol-3-one; 4-alkoxy-5-substituted-1,2-dihydro-pyrazol-3-one; 4-alkoxy-substituted-1,2-dihydro-pyrazol-3-one; 5-substituted-2H-pyrazole-3,4-dione; 5-substituted-imidazole-2,4-dione; 3-substituted-pyrrole-2,5-dione; 3-Hydroxy-4-substituted-pyrrole-2,5-dione; 3-alkoxy-4-substituted-pyrrole-2,5-dione; 3-alkoxy-substituted-pyrrole-2,5-dione; 5-substituted-oxazolidine-2,4-dione; 5-substituted-imidazolidine-2,4-dione; 5-substituted-1,2-dihydro-pyrazol-3-one; 5-substituted-2H-tetrazole; 4-substituted-2H-[1,2,3]triazole; 3-substituted-1H-[1,2,4]triazole; R or S or racemic 5-substituted-3,5-dihydro-[1,2,3]triazol-4-one; 5-substituted-2,3-dihydro-[1,2,3]triazol-4-one; R or S or racemic 4-substituted-pyrazolidine-3,5-dione; 4-substituted-[1,2,4]triazolidine-3,5-dione. Also, all benzo-fused examples of the above monocycles such as, but not limited to: 2, 3, 4 or 5-substituted-isoindole-1,3-dione; 3, 4 or 5-substituted-1,2-dihydro-indazol-3-one; 3, 4 or 5-substituted-2H-benzotriazole, and so on.

[0114] Case 3 represents compounds of the formula:



wherein the following apply:

a = 0-8; **c** = 0-8; **d** = 0-8; **f** = 0-8; **h** = 0-8; **k** = 0-8.

b = 0-4; **e** = 0-4; **i** = 0-4 (when **b, e** or **i** are =1, double bonds are either *E* or *Z*; when **b, e** or **i** are >1, any mixture of *E* or *Z* diastereomers is possible).

m = 0-4; **n** = 0-4; **q** = 0-4.

u = 0, 1; **r** = 0, 1; **p** = 0, 1; **s** = 0, 1; **t** = 0, 1; **o** = 0, 1.

R = cycloalkyl, heterocycloalkyl, alkyl, aryl, heteroaryl, R_6NH, R_6R_7N, R_8S, R_8SO, R_8SO_2, R_8SO_2NH, $R_8SO_2NR_9$, $R_{10}CO$, $R_{10}OCO$, $R_{10}NHCO$, $R_{10}R_{11}NCO$, $R_{12}O$, $R_{13}SCO$, $R_{14}NCONHR_{15}$, R_8NSO_2NH, $R_8NSO_2NR_9$, $R_{10}NCO$, $R_{10}OCONR_{16}$, $R_{10}NHCO$, $R_{10}R_{11}NCO$, $R_{13}SCONR_{17}$.

A = O, S.

$\mathbf{R^1} - \mathbf{R^{13}}$ = independently H, optionally substituted alkyl, cycloalkyl, alkylcycloalkyl, arylalkyl, aryl, heteroaryl, heterocyclic, alkylheteroaryl, alkylheterocyclic.

W = O, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, $-SO_2-$, -SONH-, -NHSO-, $-NR^1SO-$, $-SONR^1-$, $-SO_2NH-$, $-NHSO_2-$, $-NR^1SO_2-$; $-SO_2NR^1-$, $-SO_3-$ (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; $-ONR^1$; NR^1O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-; G = O, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, $-SO_2-$, -SONH-, -NHSO-, $-NR^1SO-$, $-SONR^1-$, $-SO_2NH-$, $-NHSO_2-$, $-NR^1SO_2-$; $-SO_2NR^1-$, $-SO_3-$

(sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; -ONR^1; NR^{1}O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-; **E** = O, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, -SO_2-, -SONH-, -NHSO-, -NR^{1}SO-, -SONR^1-, -SO_2NH-, -NHSO_2-, -NR^{1}SO_2-; -SO_2NR^1-, -SO_3- (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; -ONR^1; NR^{1}O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-; **J** = O, NH, NR^1 (e.g. N-Me), S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, -SO_2-, -SONH-, -NHSO-, -NR^{1}SO-, -SONR^1-, -SO_2NH-, -NHSO_2-, -NR^{1}SO_2-; -SO_2NR^1-, -SO_3- (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; -ONR^1; NR^{1}O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-.

X = H, halogen, OR^1, O, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, -SO_2-, -SONH-, -NHSO-, -NR^{1}SO-, -SONR^1-, -SO_2NH-, -NHSO_2-, -NR^{1}SO_2-; -SO_2NR^1-, -SO_3- (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; -ONR^1; NR^{1}O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-, with X attached either *meta* or *para*.

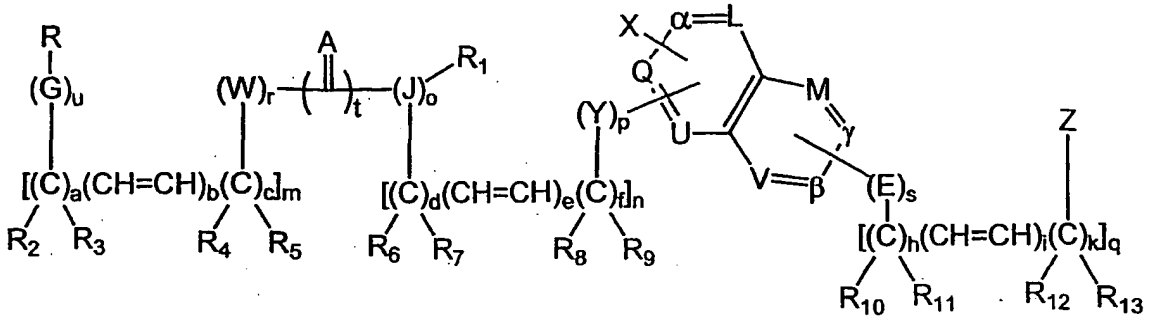
Y = H, O, OR^1, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)=O-, -SO_2-, -SONH-, -NHSO-, -NR^{1}SO-, -SONR^1-, -SO_2NH-, -NHSO_2-, -NR^{1}SO_2-; -SO_2NR^1-, -SO_3- (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; -ONR^1; NR^{1}O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-, with Y attached either *meta* or *para*.

Q,L,M, V, α, β and **U** are any combination of **Q** = CH, N, N-oxide; **L** = CH, N, N-oxide; **M** = CH, S, O, N, N-oxide, **V** = CH, S, O, N, N-oxide; α = CH, N, N-oxide; β= CH, N, S, O, N-oxide; and **U** = CH, N and N-oxide; where the point of attachment of Y and X are usually, but not necessarily, via carbon atoms in the central ring. When X = OH and L = N, a 2- or 4-pyridinol is indicated, which automatically includes the keto-tautomers, the 2- and 4- pyridones. The side chain (Y_p) can be attached, for example, via the indanoyl or benzoimidazolyl N, or at one of the remaining positions. The ring system can at its simplest be represented by

benzofused 5-membered heterocycles, such as indoles, benzoimidazoles, benzopyrrazoles, benzoisoxazole, benzofuran, benzothiophene, benzoxazole, benzothiazole, benzoisothiazole, and so on.

$Z = CO_2R^1$; *R* or *S* or racemic 5-substituted-thiazolidine-2,4-dione; *R* or *S* or racemic 3-substituted-pyrrolidine-2,5-dione; all diastereomers of 3,4-disubstituted-pyrrolidine-2,5-dione; *R* or *S* or racemic 4-substituted-azetidine-2-one; *R* or *S* or racemic 3-substituted-azetidine-2-one; all diastereomers of 3,4-disubstituted-azetidine-2-one; 3-substituted-azetidine-2,4-dione; 1-substituted-1,3-diazetidine-2,4-dione; 1-substituted-1,3-diazetidine-2-one; all diastereomers of 1,4-disubstituted-1,3-diazetidine-2-one; 5-substituted-2,4-dihydro-[1,2,4]triazol-3-one; 4-hydroxy-5-substituted-1,2-dihydro-pyrazol-3-one; 4-alkoxy-5-substituted-1,2-dihydro-pyrazol-3-one; 4-alkoxy-substituted-1,2-dihydro-pyrazol-3-one; 5-substituted-2H-pyrazole-3,4-dione; 5-substituted-imidazole-2,4-dione; 3-substituted-pyrrole-2,5-dione; 3-Hydroxy-4-substituted-pyrrole-2,5-dione; 3-alkoxy-4-substituted-pyrrole-2,5-dione; 3-alkoxy-substituted-pyrrole-2,5-dione; 5-substituted-oxazolidine-2,4-dione; 5-substituted-imidazolidine-2,4-dione; 5-substituted-1,2-dihydro-pyrazol-3-one; 5-substituted-2H-tetrazole; 4-substituted-2H-[1,2,3]triazole; 3-substituted-1H-[1,2,4]triazole; R or S or racemic 5-substituted-3,5-dihydro-[1,2,3]triazol-4-one; 5-substituted-2,3-dihydro-[1,2,3]triazol-4-one; R or S or racemic 4-substituted-pyrazolidine-3,5-dione; 4-substituted-[1,2,4]triazolidine-3,5-dione. Also, all benzo-fused examples of the above monocycles such as, but not limited to: 2, 3, 4 or 5-substituted-isoindole-1,3-dione; 3, 4 or 5-substituted-1,2-dihydro-indazol-3-one; 3, 4 or 5-substituted-2H-benzotriazole, and so on.

[0115] Case 4 represents compounds of the formula:



wherein the following apply:

a = 0-8; **c** = 0-8; **d** = 0-8; **f** = 0-8; **h** = 0-8; **k** = 0-8.

b = 0-4; **e** = 0-4; **i** = 0-4 (when **b**, **e** or **i** are =1, double bonds are either *E* or *Z*; when **b**, **e** or **i** are >1, any mixture of *E* or *Z* diastereomers is possible).

m = 0-4; **n** = 0-4; **q** = 0-4.

u = 0, 1; **r** = 0, 1; **p** = 0, 1; **s** = 0, 1; **t** = 0, 1; **o** = 0, 1.

R = cycloalkyl, heterocycloalkyl, alkyl, aryl, heteroaryl, R_6NH, R_6R_7N, R_8S, R_8SO, R_8SO_2, R_8SO_2NH, $R_8SO_2NR_9$, $R_{10}CO$, $R_{10}OCO$, $R_{10}NHCO$, $R_{10}R_{11}NCO$, $R_{12}O$, $R_{13}SCO$, $R_{14}NCONHR_{15}$, R_8NSO_2NH, $R_8NSO_2NR_9$, $R_{10}NCO$, $R_{10}OCONR_{16}$, $R_{10}NHCO$, $R_{10}R_{11}NCO$, $R_{13}SCONR_{17}$.

A = O, S.

$\mathbf{R^1 - R^{13}}$ = independently H, optionally substituted alkyl, cycloalkyl, alkylcycloalkyl, arylalkyl, aryl, heteroaryl, heterocyclic, alkylheteroaryl, alkylheterocyclic.

W = O, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, $-SO_2-$, -SONH-, -NHSO-, $-NR^1SO-$, $-SONR^1-$, $-SO_2NH-$, $-NHSO_2-$, $-NR^1SO_2-$; $-SO_2NR^1-$, $-SO_3-$ (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; -ONR^1; NR^1O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-; **G** = O, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, $-SO_2-$, -SONH-, -NHSO-, -

NR^1SO-, $-SONR^1$-, $-SO_2NH$-, $-NHSO_2$-, $-NR^1SO_2$-; $-SO_2NR^1$-, $-SO_3$- (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; $-ONR^1$; NR^1O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-; **E** = O, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, $-SO_2$-, -SONH-, -NHSO-, $-NR^1SO$-, $-SONR^1$-, $-SO_2NH$-, $-NHSO_2$-, $-NR^1SO_2$-; $-SO_2NR^1$-, $-SO_3$- (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; $-ONR^1$; NR^1O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-; **J** = O, NH, NR^1 (e.g. N-Me), S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, $-SO_2$-, -SONH-, -NHSO-, $-NR^1SO$-, $-SONR^1$-, $-SO_2NH$-, $-NHSO_2$-, $-NR^1SO_2$-; $-SO_2NR^1$-, $-SO_3$- (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; $-ONR^1$; NR^1O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-.

X = H, halogen, OR^1, O, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, $-SO_2$-, -SONH-, -NHSO-, $-NR^1SO$-, $-SONR^1$-, $-SO_2NH$-, $-NHSO_2$-, $-NR^1SO_2$-; $-SO_2NR^1$-, $-SO_3$- (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; $-ONR^1$; NR^1O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-, with X attached either *meta* or *para*.

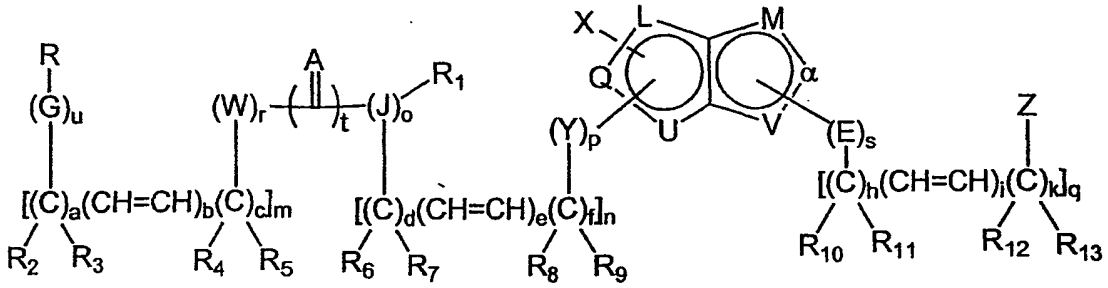
Y = H, O, OR^1, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)=O-, $-SO_2$-, -SONH-, -NHSO-, $-NR^1SO$-, $-SONR^1$-, $-SO_2NH$-, $-NHSO_2$-, $-NR^1SO_2$-; $-SO_2NR^1$-, $-SO_3$- (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; $-ONR^1$; NR^1O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-., with Y attached either *meta* or *para*.

Q,L,M, V, α, β, γ and **U** are any combination of **Q** = CH, N, N-oxide; **L** = CH, N, N-oxide; **M** = CH, N, N-oxide, **V** = CH, N, N-oxide; **α** = CH, N, N-oxide; **β** = CH, N, N-oxide; **γ** = CH, N, N-oxide; and **U** = CH, N and N-oxide; where the point of attachment of Y and X are usually via carbon atoms in the central ring. When X = OH and L = N, a 2- or 4-quinolinol is indicated, which automatically includes the keto-tautomers, the 2- and 4-quinolones. The side chain (Y_p) can be attached, for example, via the quinolinone N, or at one of the remaining positions. The ring system can

at its simplest be represented by naphthalene-based heterocycles, such as quinolines, phthalazines, quinazines, and so on.

Z = CO_2R^1; *R* or *S* or racemic 5-substituted-thiazolidine-2,4-dione; *R* or *S* or racemic 3-substituted-pyrrolidine-2,5-dione; all diastereomers of 3,4-disubstituted-pyrrolidine-2,5-dione; *R* or *S* or racemic 4-substituted-azetidine-2-one; *R* or *S* or racemic 3-substituted-azetidine-2-one; all diastereomers of 3,4-disubstituted-azetidine-2-one; 3-substituted-azetidine-2,4-dione; 1-substituted-1,3-diazetidine-2,4-dione; 1-substituted-1,3-diazetidine-2-one; all diastereomers of 1,4-disubstituted-1,3-diazetidine-2-one; 5-substituted-2,4-dihydro-[1,2,4]triazol-3-one; 4-hydroxy-5-substituted-1,2-dihydro-pyrazol-3-one; 4-alkoxy-5-substituted-1,2-dihydro-pyrazol-3-one; 4-alkoxy-substituted-1,2-dihydro-pyrazol-3-one; 5-substituted-2H-pyrazole-3,4-dione; 5-substituted-imidazole-2,4-dione; 3-substituted-pyrrole-2,5-dione; 3-Hydroxy-4-substituted-pyrrole-2,5-dione; 3-alkoxy-4-substituted-pyrrole-2,5-dione; 3-alkoxy-substituted-pyrrole-2,5-dione; 5-substituted-oxazolidine-2,4-dione; 5-substituted-imidazolidine-2,4-dione; 5-substituted-1,2-dihydro-pyrazol-3-one; 5-substituted-2H-tetrazole; 4-substituted-2H-[1,2,3]triazole; 3-substituted-1H-[1,2,4]triazole; R or S or racemic 5-substituted-3,5-dihydro-[1,2,3]triazol-4-one; 5-substituted-2,3-dihydro-[1,2,3]triazol-4-one; R or S or racemic 4-substituted-pyrazolidine-3,5-dione; 4-substituted-[1,2,4]triazolidine-3,5-dione. Also, all benzo-fused examples of the above monocycles such as, but not limited to: 2, 3, 4 or 5-substituted-isoindole-1,3-dione; 3, 4 or 5-substituted-1,2-dihydro-indazol-3-one; 3, 4 or 5-substituted-2H-benzotriazole, and so on.

[0116] Case 5 represents compounds of the formula:



wherein the following apply:

a = 0-8; **c** = 0-8; **d** = 0-8; **f** = 0-8; **h** = 0-8; **k** = 0-8.

b = 0-4; **e** = 0-4; **i** = 0-4 (when **b, e** or **i** are =1, double bonds are either *E* or *Z*; when **b, e** or **i** are >1, any mixture of *E* or *Z* diastereomers is possible).

m = 0-4; **n** = 0-4; **q** = 0-4.

u = 0, 1; **r** = 0, 1; **p** = 0, 1; **s** = 0, 1; **t** = 0, 1; **o** = 0, 1.

R = cycloalkyl, heterocycloalkyl, alkyl, aryl, heteroaryl, R_6NH, R_6R_7N, R_8S, R_8SO, R_8SO_2, R_8SO_2NH, $R_8SO_2NR_9$, $R_{10}CO$, $R_{10}OCO$, $R_{10}NHCO$, $R_{10}R_{11}NCO$, $R_{12}O$, $R_{13}SCO$, $R_{14}NCONHR_{15}$, R_8NSO_2NH, $R_8NSO_2NR_9$, $R_{10}NCO$, $R_{10}OCONR_{16}$, $R_{10}NHCO$, $R_{10}R_{11}NCO$, $R_{13}SCONR_{17}$.

A = O, S.

$\mathbf{R^1 - R^{13}}$ = independently H, optionally substituted alkyl, cycloalkyl, alkylcycloalkyl, arylalkyl, aryl, heteroaryl, heterocyclic, alkylheteroaryl, alkylheterocyclic.

W = O, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, $-SO_2-$, -SONH-, -NHSO-, $-NR^1SO-$, $-SONR^1-$, $-SO_2NH-$, $-NHSO_2-$, $-NR^1SO_2-$; $-SO_2NR^1-$, $-SO_3-$ (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; $-ONR^1$; NR^1O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-; **G** = O, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, $-SO_2-$, -SONH-, -NHSO-, -

NR^1SO-, $-SONR^1$-, $-SO_2NH$-, $-NHSO_2$-, $-NR^1SO_2$-; $-SO_2NR^1$-, $-SO_3$- (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; $-ONR^1$; NR^1O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-; **E** = O, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, $-SO_2$-, -SONH-, -NHSO-, $-NR^1SO$-, $-SONR^1$-, $-SO_2NH$-, $-NHSO_2$-, $-NR^1SO_2$-; $-SO_2NR^1$-, $-SO_3$- (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; $-ONR^1$; NR^1O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-; **J** = O, NH, NR^1 (e.g. N-Me), S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, $-SO_2$-, -SONH-, -NHSO-, $-NR^1SO$-, $-SONR^1$-, $-SO_2NH$-, $-NHSO_2$-, $-NR^1SO_2$-; $-SO_2NR^1$-, $-SO_3$- (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; $-ONR^1$; NR^1O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-.

X = H, halogen, OR^1, O, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, $-SO_2$-, -SONH-, -NHSO-, $-NR^1SO$-, $-SONR^1$-, $-SO_2NH$-, $-NHSO_2$-, $-NR^1SO_2$-; $-SO_2NR^1$-, $-SO_3$- (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; $-ONR^1$; NR^1O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-, with X attached either *meta* or *para*.

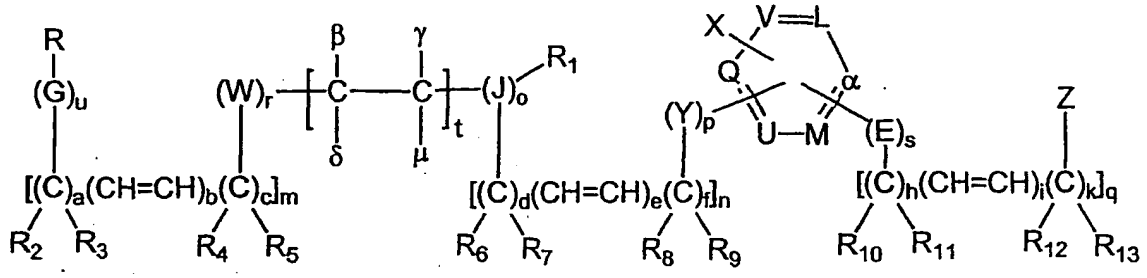
Y = H, O, OR^1, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)=O-, $-SO_2$-, -SONH-, -NHSO-, $-NR^1SO$-, $-SONR^1$-, $-SO_2NH$-, $-NHSO_2$-, $-NR^1SO_2$-; $-SO_2NR^1$-, $-SO_3$- (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; $-ONR^1$; NR^1O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-, with Y attached either *meta* or *para*.

Q,L,M, V, α, and **U** are any combination of CH, S, O, N, N-oxide. For example, when **L** and **M** are both O, a furo-[2,3-*b*]furan is indicated in which the side-chains can be attached to provide the 2,3-; 2,4-; 2,5-; or 3,4-disubstituted furo-[2,3-*b*]furans. When **M** and **U** are both O, a furo-[3,2-b]furan is indicated in which the side chains can be attached to provide the 2,3-; 2,5-; 2,6-disubstituted furo-[3,2-*b*]furans. When **L** is an oxygen atom and **M** is a nitrogen atom, the resultant heterocycle is a 6*H*-

furo[2,3-*b*]pyrrole, where substitution can occur at the 2,3-; 2,4-; 2,5-; and 2,6-positions.

Z = CO_2R^1; *R* or *S* or racemic 5-substituted-thiazolidine-2,4-dione; *R* or *S* or racemic 3-substituted-pyrrolidine-2,5-dione; all diastereomers of 3,4-disubstituted-pyrrolidine-2,5-dione; *R* or *S* or racemic 4-substituted-azetidine-2-one; *R* or *S* or racemic 3-substituted-azetidine-2-one; all diastereomers of 3,4-disubstituted-azetidine-2-one; 3-substituted-azetidine-2,4-dione; 1-substituted-1,3-diazetidine-2,4-dione; 1-substituted-1,3-diazetidine-2-one; all diastereomers of 1,4-disubstituted-1,3-diazetidine-2-one; 5-substituted-2,4-dihydro-[1,2,4]triazol-3-one; 4-hydroxy-5-substituted-1,2-dihydro-pyrazol-3-one; 4-alkoxy-5-substituted-1,2-dihydro-pyrazol-3-one; 4-alkoxy-substituted-1,2-dihydro-pyrazol-3-one; 5-substituted-2H-pyrazole-3,4-dione; 5-substituted-imidazole-2,4-dione; 3-substituted-pyrrole-2,5-dione; 3-Hydroxy-4-substituted-pyrrole-2,5-dione; 3-alkoxy-4-substituted-pyrrole-2,5-dione; 3-alkoxy-substituted-pyrrole-2,5-dione; 5-substituted-oxazolidine-2,4-dione; 5-substituted-imidazolidine-2,4-dione; 5-substituted-1,2-dihydro-pyrazol-3-one; 5-substituted-2H-tetrazole; 4-substituted-2H-[1,2,3]triazole; 3-substituted-1H-[1,2,4]triazole; R or S or racemic 5-substituted-3,5-dihydro-[1,2,3]triazol-4-one; 5-substituted-2,3-dihydro-[1,2,3]triazol-4-one; R or S or racemic 4-substituted-pyrazolidine-3,5-dione; 4-substituted-[1,2,4]triazolidine-3,5-dione. Also, all benzo-fused examples of the above monocycles such as, but not limited to: 2, 3, 4 or 5-substituted-isoindole-1,3-dione; 3, 4 or 5-substituted-1,2-dihydro-indazol-3-one; 3, 4 or 5-substituted-2H-benzotriazole, and so on.

[0117] Case 6 represents compounds of the formula:



wherein the following apply:

a = 0-8; **c** = 0-8; **d** = 0-8; **f** = 0-8; **h** = 0-8; **k** = 0-8.

b = 0-4; **e** = 0-4; **i** = 0-4 (when **b**, **e** or **i** are = 1, double bonds are either *E* or *Z*; when **b**, **e** or **i** are >1, any mixture of *E* or *Z* diastereomers is possible).

m = 0-4; **n** = 0-4; **q** = 0-4.

u = 0, 1; **r** = 0, 1; **p** = 0, 1; **s** = 0, 1; **t** = 0, 1; **o** = 0, 1.

R = cycloalkyl, heterocycloalkyl, alkyl, aryl, heteroaryl, R_6NH, R_6R_7N, R_8S, R_8SO, R_8SO_2, R_8SO_2NH, $R_8SO_2NR_9$, $R_{10}CO$, $R_{10}OCO$, $R_{10}NHCO$, $R_{10}R_{11}NCO$, $R_{12}O$, $R_{13}SCO$, $R_{14}NCONHR_{15}$, R_8NSO_2NH, $R_8NSO_2NR_9$, $R_{10}NCO$, $R_{10}OCONR_{16}$, $R_{10}NHCO$, $R_{10}R_{11}NCO$, $R_{13}SCONR_{17}$.

A = O, S.

$\mathbf{R^1} - \mathbf{R^{13}}$ = independently H, optionally substituted alkyl, cycloalkyl, alkylcycloalkyl, arylalkyl, aryl, heteroaryl, heterocyclic, alkylheteroaryl, alkylheterocyclic.

W = O, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, $-SO_2-$, -SONH-, -NHSO-, $-NR^1SO-$, $-SONR^1-$, $-SO_2NH-$, $-NHSO_2-$, $-NR^1SO_2-$; $-SO_2NR^1-$, $-SO_3-$ (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; -ONR^1; NR^1O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-; **G** = O, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, $-SO_2-$, -SONH-, -NHSO-, $-NR^1SO-$, $-SONR^1-$, $-SO_2NH-$, $-NHSO_2-$, $-NR^1SO_2-$; $-SO_2NR^1-$, $-SO_3-$

(sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; -ONR^1; NR^{1}O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-; **E** = O, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, -SO_2-, -SONH-, -NHSO-, -NR^{1}SO-, -SONR^1-, -SO_2NH-, -NHSO_2-, -NR^{1}SO_2-; -SO_2NR^1-, -SO_3- (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; -ONR^1; NR^{1}O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-; **J** = O, NH, NR^1 (e.g. N-Me), S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, -SO_2-, -SONH-, -NHSO-, -NR^{1}SO-, -SONR^1-, -SO_2NH-, -NHSO_2-, -NR^{1}SO_2-; -SO_2NR^1-, -SO_3- (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; -ONR^1; NR^{1}O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-.

X = H, halogen, OR^1, O, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, -SO_2-, -SONH-, -NHSO-, -NR^{1}SO-, -SONR^1-, -SO_2NH-, -NHSO_2-, -NR^{1}SO_2-; -SO_2NR^1-, -SO_3- (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; -ONR^1; NR^{1}O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-, with X attached either *meta* or *para*.

Y = H, O, OR^1, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)=O-, -SO_2-, -SONH-, -NHSO-, -NR^{1}SO-, -SONR^1-, -SO_2NH-, -NHSO_2-, -NR^{1}SO_2-; -SO_2NR^1-, -SO_3- (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; -ONR^1; NR^{1}O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-, with Y attached either *meta* or *para*.

Q,L,M, V, α, and **U** are any combination of **Q** = CH, N, N-oxide; **L** = CH, N, N-oxide; **M** = CH, N, N-oxide, **V** = CH, N, N-oxide, **α** = CH, N, N-oxide, and **U** = CH, N and N-oxide; where the point of attachment of Y and X are usually via carbon atoms in the central ring. When X = OH and L = N, a 2- or 4-pyridinol is indicated, which automatically includes the keto-tautomers, the 2- and 4- pyridones. The side chain (Y_p) can be attached via the pyridone N, or at one of the remaining positions. Also, the ring can be benzenoid, pyridinoid, pyrimidinoid, and so on where benzenoid is preferred.

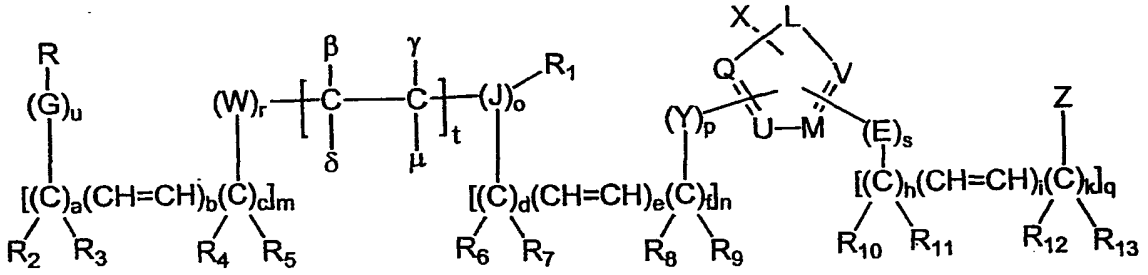
Z = CO_2R^1; *R* or *S* or racemic 5-substituted-thiazolidine-2,4-dione; *R* or *S* or racemic 3-substituted-pyrrolidine-2,5-dione; all diastereomers of 3,4-disubstituted-pyrrolidine-2,5-dione; *R* or *S* or racemic 4-substituted-azetidine-2-one; *R* or *S* or racemic 3-substituted-azetidine-2-one; all diastereomers of 3,4-disubstituted-azetidine-2-one; 3-substituted-azetidine-2,4-dione; 1-substituted-1,3-diazetidine-2,4-dione; 1-substituted-1,3-diazetidine-2-one; all diastereomers of 1,4-disubstituted-1,3-diazetidine-2-one; 5-substituted-2,4-dihydro-[1,2,4]triazol-3-one; 4-hydroxy-5-substituted-1,2-dihydro-pyrazol-3-one; 4-alkoxy-5-substituted-1,2-dihydro-pyrazol-3-one; 4-alkoxy-substituted-1,2-dihydro-pyrazol-3-one; 5-substituted-2H-pyrazole-3,4-dione; 5-substituted-imidazole-2,4-dione; 3-substituted-pyrrole-2,5-dione; 3-Hydroxy-4-substituted-pyrrole-2,5-dione; 3-alkoxy-4-substituted-pyrrole-2,5-dione; 3-alkoxy-substituted-pyrrole-2,5-dione; 5-substituted-oxazolidine-2,4-dione; 5-substituted-imidazolidine-2,4-dione; 5-substituted-1,2-dihydro-pyrazol-3-one; 5-substituted-2H-tetrazole; 4-substituted-2H-[1,2,3]triazole; 3-substituted-1H-[1,2,4]triazole; R or S or racemic 5-substituted-3,5-dihydro-[1,2,3]triazol-4-one; 5-substituted-2,3-dihydro-[1,2,3]triazol-4-one; R or S or racemic 4-substituted-pyrazolidine-3,5-dione; 4-substituted-[1,2,4]triazolidine-3,5-dione. Also, all benzo-fused examples of the above monocycles such as, but not limited to: 2, 3, 4 or 5-substituted-isoindole-1,3-dione; 3, 4 or 5-substituted-1,2-dihydro-indazol-3-one; 3, 4 or 5-substituted-2H-benzotriazole, and so on.

When t = 1, one of β or γ is either CH_2, O, N, or S and together with the other, form a cis or trans cyclopropane, epoxide, aziridine, or episulfide. Concurrently, δ and μ are either cis or trans to one another, and can be any combination of H, alkyl, cycloalkyl, aryl, heterocyclic, heteroaryl, alkylaryl, alkylcycloalkyl, alkylheterocyclic, alkylheteroaryl, and

optionally substituted derivatives therein. Preferred in this arrangement is the cis-cyclopropyl compound.

When **t** = 1, together β and γ form a second bond that is either cis or trans (*E* or *Z*) such that the overall unit enclosed by **t** is a double bond. Concurrently, δ and μ are either cis or trans to one another, and can be any combination of H, alkyl, alkoxyl, halogen, thioalkoxyl, acyloxyl, cycloalkyl, aryl, heterocyclic, heteroaryl, alkylaryl, alkylcycloalkyl, alkylheterocyclic, alkylheteroaryl, and optionally substituted derivatives therein. Alternatively, together β and γ form a second bond while concurrently, δ and μ form a third bond such that the entire unit enclosed by **t** is a triple bond (alkyne). Preferred in this arrangement is the *Z*-double bond. Another example is exemplified when the Z-double bond is substituted by δ and μ such that together they form a ring. This ring can be benzenoid, heterocyclic, heteroaryl, and so on.

[0118] Case 7 represents compounds of the formula:



wherein the following apply:

a = 0-8; **c** = 0-8; **d** = 0-8; **f** = 0-8; **h** = 0-8; **k** = 0-8.

b = 0-4; **e** = 0-4; **i** = 0-4 (when **b**, **e** or **i** are = 1, double bonds are either *E* or *Z*; when **b**, **e** or **i** are >1, any mixture of *E* or *Z* diastereomers is possible).

m = 0-4; **n** = 0-4; **q** = 0-4.

u = 0, 1; **r** = 0, 1; **p** = 0, 1; **s** = 0, 1; **t** = 0, 1; **o** = 0, 1.

R = cycloalkyl, heterocycloalkyl, alkyl, aryl, heteroaryl, R_6NH, R_6R_7N, R_8S, R_8SO, R_8SO_2, R_8SO_2NH, $R_8SO_2NR_9$, $R_{10}CO$, $R_{10}OCO$, $R_{10}NHCO$, $R_{10}R_{11}NCO$, $R_{12}O$, $R_{13}SCO$, $R_{14}NCONHR_{15}$, R_8NSO_2NH, $R_8NSO_2NR_9$, $R_{10}NCO$, $R_{10}OCONR_{16}$, $R_{10}NHCO$, $R_{10}R_{11}NCO$, $R_{13}SCONR_{17}$.

A = O, S.

$\mathbf{R^1} - \mathbf{R^{13}}$ = independently H, optionally substituted alkyl, cycloalkyl, alkylcycloalkyl, arylalkyl, aryl, heteroaryl, heterocyclic, alkylheteroaryl, alkylheterocyclic.

W = O, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, $-SO_2-$, -SONH-, -NHSO-, $-NR^1SO-$, $-SONR^1-$, $-SO_2NH-$, $-NHSO_2-$, $-NR^1SO_2-$; $-SO_2NR^1-$, $-SO_3-$ (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; $-ONR^1$; NR^1O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-; **G** = O, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, $-SO_2-$, -SONH-, -NHSO-, $-NR^1SO-$, $-SONR^1-$, $-SO_2NH-$, $-NHSO_2-$, $-NR^1SO_2-$; $-SO_2NR^1-$, $-SO_3-$ (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; $-ONR^1$; NR^1O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-; **E** = O, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, $-SO_2-$, -SONH-, -NHSO-, $-NR^1SO-$, $-SONR^1-$, $-SO_2NH-$, $-NHSO_2-$, $-NR^1SO_2-$; $-SO_2NR^1-$, $-SO_3-$ (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; $-ONR^1$; NR^1O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-; **J** = O, NH, NR^1 (e.g. N-Me), S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, $-SO_2-$, -SONH-, -NHSO-, $-NR^1SO-$, $-SONR^1-$, $-SO_2NH-$, $-NHSO_2-$, $-NR^1SO_2-$; $-SO_2NR^1-$, $-SO_3-$ (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; $-ONR^1$; NR^1O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-.

X = H, halogen, OR^1, O, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, $-SO_2-$, -SONH-, -NHSO-, $-NR^1SO-$, $-SONR^1-$, $-SO_2NH-$, $-NHSO_2-$, $-NR^1SO_2-$; $-SO_2NR^1-$, $-SO_3-$ (sulfonate), C=O, -NHNH-, -N=N-,

-NHO-, -ONH-; -ONR^1; NR^{1}O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-, with X attached either *meta* or *para*.

Y = H, O, OR^1, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)=O-, -SO_2-, -SONH-, -NHSO-, -NR^{1}SO-, -SONR^1-, -SO_2NH-, -NHSO$_2$-, -NR^{1}SO$_2$-; -SO_2NR^1-, -SO_3- (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; -ONR^1; NR^{1}O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-., with Y attached either *meta* or *para*.

Q,L,M,V and **U** are any combination of **Q** = CH, N, N-oxide; **L** = C=O, O, S, SO, SO_2, N, NR, NH, N-oxide; **M** = CH, N, N-oxide, **U** = CH, N and N-oxide; and **V** = CH, N and N-oxide; where the point of attachment of Y and X are usually via carbon atoms in the central ring. When X = OH and L = N, a 2- or 3-pyrrolinol is indicated, which automatically includes the keto-tautomers, the 1,5-dihydropyrrol-2-one and 1,2-dihydropyrrol-3-one. The side chain (Y_p) can be attached via the pyrrolone N, or at one of the remaining positions. Also, the ring can contain multiple heteroatoms such as would be the case for: histidinoid, pyrrazoloid, triazoloid, tetrazoloid, and so on, where thiazoloid or isothiazoloid is preferred.

Z = CO_2R^1; *R* or *S* or racemic 5-substituted-thiazolidine-2,4-dione; *R* or *S* or racemic 3-substituted-pyrrolidine-2,5-dione; all diastereomers of 3,4-disubstituted-pyrrolidine-2,5-dione; *R* or *S* or racemic 4-substituted-azetidine-2-one; *R* or *S* or racemic 3-substituted-azetidine-2-one; all diastereomers of 3,4-disubstituted-azetidine-2-one; 3-substituted-azetidine-2,4-dione; 1-substituted-1,3-diazetidine-2,4-dione; 1-substituted-1,3-diazetidine-2-one; all diastereomers of 1,4-disubstituted-1,3-diazetidine-2-one; 5-substituted-2,4-dihydro-[1,2,4]triazol-3-one; 4-hydroxy-5-substituted-1,2-dihydro-pyrazol-3-one; 4-alkoxy-5-substituted-1,2-dihydro-pyrazol-3-one; 4-alkoxy-substituted-1,2-dihydro-pyrazol-3-one; 5-substituted-2H-pyrazole-3,4-dione; 5-substituted-imidazole-2,4-

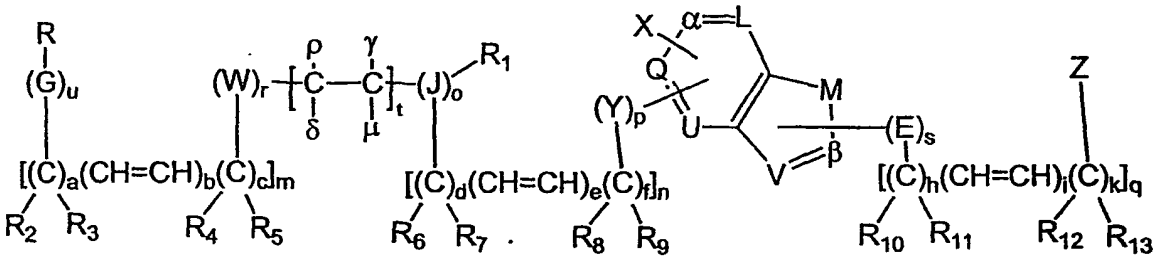
dione; 3-substituted-pyrrole-2,5-dione; 3-Hydroxy-4-substituted-pyrrole-2,5-dione; 3-alkoxy-4-substituted-pyrrole-2,5-dione; 3-alkoxy-substituted-pyrrole-2,5-dione; 5-substituted-oxazolidine-2,4-dione; 5-substituted-imidazolidine-2,4-dione; 5-substituted-1,2-dihydro-pyrazol-3-one; 5-substituted-2H-tetrazole; 4-substituted-2H-[1,2,3]triazole; 3-substituted-1H-[1,2,4]triazole; R or S or racemic 5-substituted-3,5-dihydro-[1,2,3]triazol-4-one; 5-substituted-2,3-dihydro-[1,2,3]triazol-4-one; R or S or racemic 4-substituted-pyrazolidine-3,5-dione; 4-substituted-[1,2,4]triazolidine-3,5-dione. Also, all benzo-fused examples of the above monocycles such as, but not limited to: 2, 3, 4 or 5-substituted-isoindole-1,3-dione; 3, 4 or 5-substituted-1,2-dihydro-indazol-3-one; 3, 4 or 5-substituted-2H-benzotriazole, and so on.

When **t** = 1, one of β or γ is either CH_2, O, N, or S and together with the other, form a cis or trans cyclopropane, epoxide, aziridine, or episulfide. Concurrently, δ and μ are either cis or trans to one another, and can be any combination of H, alkyl, cycloalkyl, aryl, heterocyclic, heteroaryl, alkylaryl, alkylcycloalkyl, alkylheterocyclic, alkylheteroaryl, and optionally substituted derivatives therein. Preferred in this arrangement is the cis-cyclopropyl compound.

When **t** = 1, together β and γ form a second bond that is either cis or trans (*E* or *Z*) such that the overall unit enclosed by **t** is a double bond. Concurrently, δ and μ are either cis or trans to one another, and can be any combination of H, alkyl, alkoxyl, halogen, thioalkoxyl, acyloxyl, cycloalkyl, aryl, heterocyclic, heteroaryl, alkylaryl, alkylcycloalkyl, alkylheterocyclic, alkylheteroaryl, and optionally substituted derivatives therein. Alternatively, together β and γ form a second bond while concurrently, δ and μ form a third bond such that the entire unit enclosed by **t** is a triple bond (alkyne). Preferred in this arrangement is the *Z*-

double bond. Another example is exemplified when the Z-double bond is substituted by δ and μ such that together they form a ring. This ring can be benzenoid, heterocyclic, heteroaryl, and so on.

[0119] Case 8 represents compounds of the formula:



wherein the following apply:

a = 0-8; **c** = 0-8; **d** = 0-8; **f** = 0-8; **h** = 0-8; **k** = 0-8.

b = 0-4; **e** = 0-4; **i** = 0-4 (when **b**, **e** or **i** are =1, double bonds are either *E* or *Z*; when **b**, **e** or **i** are >1, any mixture of *E* or *Z* diastereomers is possible).

m = 0-4; **n** = 0-4; **q** = 0-4.

u = 0, 1; **r** = 0, 1; **p** = 0, 1; **s** = 0, 1; **t** = 0, 1; **o** = 0, 1.

R = cycloalkyl, heterocycloalkyl, alkyl, aryl, heteroaryl, R_6NH, R_6R_7N, R_8S, R_8SO, R_8SO_2, R_8SO_2NH, $R_8SO_2NR_9$, $R_{10}CO$, $R_{10}OCO$, $R_{10}NHCO$, $R_{10}R_{11}NCO$, $R_{12}O$, $R_{13}SCO$, $R_{14}NCONHR_{15}$, R_8NSO_2NH, $R_8NSO_2NR_9$, $R_{10}NCO$, $R_{10}OCONR_{16}$, $R_{10}NHCO$, $R_{10}R_{11}NCO$, $R_{13}SCONR_{17}$.

A = O, S.

$\mathbf{R^1} - \mathbf{R^{13}}$ = independently H, optionally substituted alkyl, cycloalkyl, alkylcycloalkyl, arylalkyl, aryl, heteroaryl, heterocyclic, alkylheteroaryl, alkylheterocyclic.

W = O, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, -SO_2-, -SONH-, -NHSO-, -NR^1SO-, -$SONR^1$-, -SO_2NH-, -$NHSO_2$-, -NR^1SO_2-; -

SO_2NR^1-, -SO_3- (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; -ONR^1; NR^1O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-; **G** = O, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, -SO_2-, -SONH-, -NHSO-, -NR^1SO-, -$SONR^1$-, -SO_2NH-, -$NHSO_2$-, -NR^1SO_2-; -SO_2NR^1-, -SO_3- (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; -ONR^1; NR^1O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-; **E** = O, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, -SO_2-, -SONH-, -NHSO-, -NR^1SO-, -$SONR^1$-, -SO_2NH-, -$NHSO_2$-, -NR^1SO_2-; -SO_2NR^1-, -SO_3- (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; -ONR^1; NR^1O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-; **J** = O, NH, NR^1 (e.g. N-Me), S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, -SO_2-, -SONH-, -NHSO-, -NR^1SO-, -$SONR^1$-, -SO_2NH-, -$NHSO_2$-, -NR^1SO_2-; -SO_2NR^1-, -SO_3- (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; -ONR^1; NR^1O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-.

X = H, halogen, OR^1, O, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, -SO_2-, -SONH-, -NHSO-, -NR^1SO-, -$SONR^1$-, -SO_2NH-, -$NHSO_2$-, -NR^1SO_2-; -SO_2NR^1-, -SO_3- (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; -ONR^1; NR^1O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-, with X attached either *meta* or *para*.

Y = H, O, OR^1, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)=O-, -SO_2-, -SONH-, -NHSO-, -NR^1SO-, -$SONR^1$-, -SO_2NH-, -$NHSO_2$-, -NR^1SO_2-; -SO_2NR^1-, -SO_3- (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; -ONR^1; NR^1O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-, with Y attached either *meta* or *para*.

Q,L,M, V, α, β and **U** are any combination of **Q** = CH, N, N-oxide; **L** = CH, N, N-oxide; **M** = CH, S, O, N; N-oxide, **V** = CH, S, O, N, N-oxide; α = CH, N, S, O, N-oxide; β = CH, N, S, O, N-oxide; and **U** = CH, N and N-oxide; where the point of attachment of Y and X are usually via carbon atoms in the central ring. When X = OH and L = N, a 2- or 4-pyridinol is

indicated, which automatically includes the keto-tautomers, the 2- and 4-pyridones. The side chain (Y_p) can be attached, for example, via the indanoyl or benzoimidazolyl N, or at one of the remaining positions. The ring system can at its simplest be represented by benzofused 5-membered heterocycles, such as indoles, benzoimidazoles, benzopyrrazoles, benzoisoxazole, benzofuran, benzothiophene, benzoxazole, benzothiazole, benzoisothiazole, and so on.

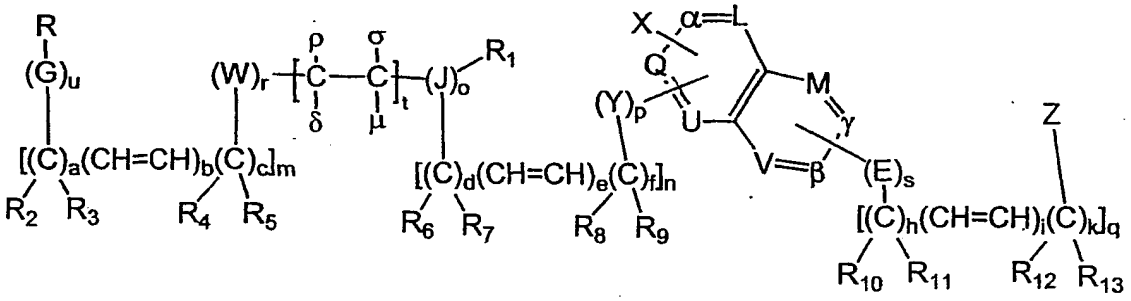
Z = CO_2R^1; *R* or *S* or racemic 5-substituted-thiazolidine-2,4-dione; *R* or *S* or racemic 3-substituted-pyrrolidine-2,5-dione; all diastereomers of 3,4-disubstituted-pyrrolidine-2,5-dione; *R* or *S* or racemic 4-substituted-azetidine-2-one; *R* or *S* or racemic 3-substituted-azetidine-2-one; all diastereomers of 3,4-disubstituted-azetidine-2-one; 3-substituted-azetidine-2,4-dione; 1-substituted-1,3-diazetidine-2,4-dione; 1-substituted-1,3-diazetidine-2-one; all diastereomers of 1,4-disubstituted-1,3-diazetidine-2-one; 5-substituted-2,4-dihydro-[1,2,4]triazol-3-one; 4-hydroxy-5-substituted-1,2-dihydro-pyrazol-3-one; 4-alkoxy-5-substituted-1,2-dihydro-pyrazol-3-one; 4-alkoxy-substituted-1,2-dihydro-pyrazol-3-one; 5-substituted-2H-pyrazole-3,4-dione; 5-substituted-imidazole-2,4-dione; 3-substituted-pyrrole-2,5-dione; 3-Hydroxy-4-substituted-pyrrole-2,5-dione; 3-alkoxy-4-substituted-pyrrole-2,5-dione; 3-alkoxy-substituted-pyrrole-2,5-dione; 5-substituted-oxazolidine-2,4-dione; 5-substituted-imidazolidine-2,4-dione; 5-substituted-1,2-dihydro-pyrazol-3-one; 5-substituted-2H-tetrazole; 4-substituted-2H-[1,2,3]triazole; 3-substituted-1H-[1,2,4]triazole; R or S or racemic 5-substituted-3,5-dihydro-[1,2,3]triazol-4-one; 5-substituted-2,3-dihydro-[1,2,3]triazol-4-one; R or S or racemic 4-substituted-pyrazolidine-3,5-dione; 4-substituted-[1,2,4]triazolidine-3,5-dione. Also, all benzo-fused examples of the above monocycles such as, but not limited to: 2, 3, 4 or 5-substituted-isoindole-

1,3-dione; 3, 4 or 5-substituted-1,2-dihydro-indazol-3-one; 3, 4 or 5-substituted-2H-benzotriazole, and so on.

When **t** = 1, one of ρ or γ is either CH_2, O, N, or S and together with the other, form a cis or trans cyclopropane, epoxide, aziridine, or episulfide. Concurrently, δ and μ are either cis or trans to one another, and can be any combination of H, alkyl, cycloalkyl, aryl, heterocyclic, heteroaryl, alkylaryl, alkylcycloalkyl, alkylheterocyclic, alkylheteroaryl, and optionally substituted derivatives therein. Preferred in this arrangement is the cis-cyclopropyl compound.

When **t** = 1, together ρ and γ form a second bond that is either cis or trans (*E* or *Z*) such that the overall unit enclosed by **t** is a double bond. Concurrently, δ and μ are either cis or trans to one another, and can be any combination of H, alkyl, alkoxyl, halogen, thioalkoxyl, acyloxyl, cycloalkyl, aryl, heterocyclic, heteroaryl, alkylaryl, alkylcycloalkyl, alkylheterocyclic, alkylheteroaryl, and optionally substituted derivatives therein. Alternatively, together ρ and γ form a second bond while concurrently, δ and μ form a third bond such that the entire unit enclosed by **t** is a triple bond (alkyne). Preferred in this arrangement is the *Z*-double bond. Another example is exemplified when the Z-double bond is substituted by δ and μ such that together they form a ring. This ring can be benzenoid, heterocyclic, heteroaryl, and so on.

[0120] Case 9 represents compounds of the formula:



wherein the following apply:

a = 0-8; **c** = 0-8; **d** = 0-8; **f** = 0-8; **h** = 0-8; **k** = 0-8.

b = 0-4; **e** = 0-4; **i** = 0-4 (when **b, e** or **i** are =1, double bonds are either *E* or *Z*; when **b, e** or **i** are >1, any mixture of *E* or *Z* diastereomers is possible).

m = 0-4; **n** = 0-4; **q** = 0-4.

u = 0, 1; **r** = 0, 1; **p** = 0, 1; **s** = 0, 1; **t** = 0, 1; **o** = 0, 1.

R = cycloalkyl, heterocycloalkyl, alkyl, aryl, heteroaryl, R_6NH, R_6R_7N, R_8S, R_8SO, R_8SO_2, R_8SO_2NH, $R_8SO_2NR_9$, $R_{10}CO$, $R_{10}OCO$, $R_{10}NHCO$, $R_{10}R_{11}NCO$, $R_{12}O$, $R_{13}SCO$, $R_{14}NCONHR_{15}$, R_8NSO_2NH, $R_8NSO_2NR_9$, $R_{10}NCO$, $R_{10}OCONR_{16}$, $R_{10}NHCO$, $R_{10}R_{11}NCO$, $R_{13}SCONR_{17}$.

A = O, S.

$\mathbf{R^1} - \mathbf{R^{13}}$ = independently H, optionally substituted alkyl, cycloalkyl, alkylcycloalkyl, arylalkyl, aryl, heteroaryl, heterocyclic, alkylheteroaryl, alkylheterocyclic.

W = O, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, $-SO_2-$, -SONH-, -NHSO-, $-NR^1SO-$, $-SONR^1-$, $-SO_2NH-$, $-NHSO_2-$, $-NR^1SO_2-$; $-SO_2NR^1-$, $-SO_3-$ (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; $-ONR^1$; NR^1O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-; **G** = O, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, $-SO_2-$, -SONH-, -NHSO-, $-NR^1SO-$, $-SONR^1-$, $-SO_2NH-$, $-NHSO_2-$, $-NR^1SO_2-$; $-SO_2NR^1-$, $-SO_3-$ (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; $-ONR^1$; NR^1O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-; **E** = O, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, $-SO_2-$, -SONH-, -NHSO-, $-NR^1SO-$, $-SONR^1-$, $-SO_2NH-$, $-NHSO_2-$, $-NR^1SO_2-$; $-SO_2NR^1-$, $-SO_3-$ (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; $-ONR^1$; NR^1O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-; **J** = O, NH, NR^1 (e.g. N-Me), S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, $-SO_2-$, -SONH-, -NHSO-, $-NR^1SO-$, $-SONR^1-$, -

SO_2NH-, -$NHSO_2$-, -NR^1SO_2-; -SO_2NR^1-, -SO_3- (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; -ONR^1; NR^1O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-.

X = H, halogen, OR^1, O, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, -SO_2-, -SONH-, -NHSO-, -NR^1SO-, -$SONR^1$-, -SO_2NH-, -$NHSO_2$-, -NR^1SO_2-; -SO_2NR^1-, -SO_3- (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; -ONR^1; NR^1O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-, with X attached either *meta* or *para*.

Y = H, O, OR^1, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)=O-, -SO_2-, -SONH-, -NHSO-, -NR^1SO-, -$SONR^1$-, -SO_2NH-, -$NHSO_2$-, -NR^1SO_2-; -SO_2NR^1-, -SO_3- (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; -ONR^1; NR^1O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-, with Y attached either *meta* or *para*.

Q,L,M, V, α, β, γ and **U** are any combination of **Q** = CH, N, N-oxide; **L** = CH, N, N-oxide; **M** = CH, N, N-oxide, **V** = CH, N, N-oxide; **α** = CH, N, N-oxide; **β** = CH, N, N-oxide; **γ** = CH, N, N-oxide; and **U** = CH, N and N-oxide; where the point of attachment of Y and X are usually, but not necessarily, via carbon atoms in the central ring. When X = OH and L = N, a 2- or 4-quinolinol is indicated, which automatically includes the keto-tautomers, the 2- and 4- quinolones. The side chain (Y_p) can be attached, for example, via the quinolinone N, or at one of the remaining positions. The ring system can at its simplest be represented by naphthalene-based heterocycles, such as quinolines, phthalazines, quinazines, and so on.

Z = CO_2R^1; *R* or *S* or racemic 5-substituted-thiazolidine-2,4-dione; *R* or *S* or racemic 3-substituted-pyrrolidine-2,5-dione; all diastereomers of 3,4-disubstituted-pyrrolidine-2,5-dione; *R* or *S* or racemic 4-substituted-azetidine-2-one; *R* or *S* or racemic 3-substituted-azetidine-2-one; all diastereomers of 3,4-disubstituted-azetidine-2-one; 3-substituted-azetidine-2,4-dione; 1-substituted-1,3-diazetidine-2,4-dione; 1-substituted-

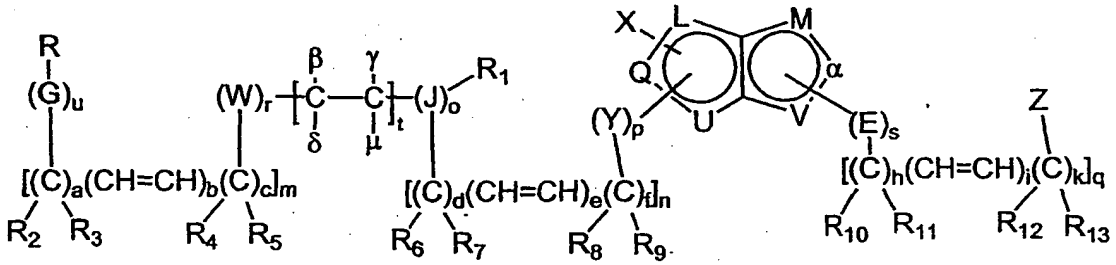
1,3-diazetidine-2-one; all diastereomers of 1,4-disubstituted-1,3-diazetidine-2-one; 5-substituted-2,4-dihydro-[1,2,4]triazol-3-one; 4-hydroxy-5-substituted-1,2-dihydro-pyrazol-3-one; 4-alkoxy-5-substituted-1,2-dihydro-pyrazol-3-one; 4-alkoxy-substituted-1,2-dihydro-pyrazol-3-one; 5-substituted-2H-pyrazole-3,4-dione; 5-substituted-imidazole-2,4-dione; 3-substituted-pyrrole-2,5-dione; 3-Hydroxy-4-substituted-pyrrole-2,5-dione; 3-alkoxy-4-substituted-pyrrole-2,5-dione; 3-alkoxy-substituted-pyrrole-2,5-dione; 5-substituted-oxazolidine-2,4-dione; 5-substituted-imidazolidine-2,4-dione; 5-substituted-1,2-dihydro-pyrazol-3-one; 5-substituted-2H-tetrazole; 4-substituted-2H-[1,2,3]triazole; 3-substituted-1H-[1,2,4]triazole; R or S or racemic 5-substituted-3,5-dihydro-[1,2,3]triazol-4-one; 5-substituted-2,3-dihydro-[1,2,3]triazol-4-one; R or S or racemic 4-substituted-pyrazolidine-3,5-dione; 4-substituted-[1,2,4]triazolidine-3,5-dione. Also, all benzo-fused examples of the above monocycles such as, but not limited to: 2, 3, 4 or 5-substituted-isoindole-1,3-dione; 3, 4 or 5-substituted-1,2-dihydro-indazol-3-one; 3, 4 or 5-substituted-2H-benzotriazole, and so on.

When **t** = 1, one of ρ or σ is either CH_2, O, N, or S and together with the other, form a cis or trans cyclopropane, epoxide, aziridine, or episulfide. Concurrently, δ and μ are either cis or trans to one another, and can be any combination of H, alkyl, cycloalkyl, aryl, heterocyclic, heteroaryl, alkylaryl, alkylcycloalkyl, alkylheterocyclic, alkylheteroaryl, and optionally substituted derivatives therein. Preferred in this arrangement is the cis-cyclopropyl compound.

When **t** = 1, together ρ and σ form a second bond that is either cis or trans (*E* or *Z*) such that the overall unit enclosed by **t** is a double bond. Concurrently, δ and μ are either cis or trans to one another, and can be any combination of H, alkyl, alkoxyl, halogen, thioalkoxyl, acyloxyl, cycloalkyl, aryl, heterocyclic, heteroaryl, alkylaryl, alkylcycloalkyl,

alkylheterocyclic, alkylheteroaryl, and optionally substituted derivatives therein. Alternatively, together ρ and σ form a second bond while concurrently, δ and μ form a third bond such that the entire unit enclosed by **t** is a triple bond (alkyne). Preferred in this arrangement is the *Z*-double bond. Another example is exemplified when the Z-double bond is substituted by δ and μ such that together they form a ring. This ring can be benzenoid, heterocyclic, heteroaryl, and so on.

[0121] Case 10 represents compounds of the formula:



wherein the following apply:

a = 0-8; **c** = 0-8; **d** = 0-8; **f** = 0-8; **h** = 0-8; **k** = 0-8.

b = 0-4; **e** = 0-4; **i** = 0-4 (when **b, e** or **i** are =1, double bonds are either *E* or *Z*; when **b, e** or **i** are >1, any mixture of *E* or *Z* diastereomers is possible).

m = 0-4; **n** = 0-4; **q** = 0-4.

u = 0, 1; **r** = 0, 1; **p** = 0, 1; **s** = 0, 1; **t** = 0, 1; **o** = 0, 1.

R = cycloalkyl, heterocycloalkyl, alkyl, aryl, heteroaryl, R_6NH, R_6R_7N, R_8S, R_8SO, R_8SO_2, R_8SO_2NH, $R_8SO_2NR_9$, $R_{10}CO$, $R_{10}OCO$, $R_{10}NHCO$, $R_{10}R_{11}NCO$, $R_{12}O$, $R_{13}SCO$, $R_{14}NCONHR_{15}$, R_8NSO_2NH, $R_8NSO_2NR_9$, $R_{10}NCO$, $R_{10}OCONR_{16}$, $R_{10}NHCO$, $R_{10}R_{11}NCO$, $R_{13}SCONR_{17}$.

A = O, S.

$R^1 - R^{13}$ = independently H, optionally substituted alkyl, cycloalkyl, alkylcycloalkyl, arylalkyl, aryl, heteroaryl, heterocyclic, alkylheteroaryl, alkylheterocyclic.

W = O, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, $-SO_2-$, -SONH-, -NHSO-, $-NR^1SO-$, $-SONR^1-$, $-SO_2NH-$, $-NHSO_2-$, $-NR^1SO_2-$; $-SO_2NR^1-$, $-SO_3-$ (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; $-ONR^1$; NR^1O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-; G = O, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, $-SO_2-$, -SONH-, -NHSO-, $-NR^1SO-$, $-SONR^1-$, $-SO_2NH-$, $-NHSO_2-$, $-NR^1SO_2-$; $-SO_2NR^1-$, $-SO_3-$ (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; $-ONR^1$; NR^1O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-;

E = O, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, $-SO_2-$, -SONH-, -NHSO-, $-NR^1SO-$, $-SONR^1-$, $-SO_2NH-$, $-NHSO_2-$, $-NR^1SO_2-$; $-SO_2NR^1-$, $-SO_3-$ (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; $-ONR^1$; NR^1O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-;

J = O, NH, NR^1 (e.g. N-Me), S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, $-SO_2-$, -SONH-, -NHSO-, $-NR^1SO-$, $-SONR^1-$, $-SO_2NH-$, $-NHSO_2-$, $-NR^1SO_2-$; $-SO_2NR^1-$, $-SO_3-$ (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; $-ONR^1$; NR^1O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-.

X = H, halogen, OR^1, O, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)O-, $-SO_2-$, -SONH-, -NHSO-, $-NR^1SO-$, $-SONR^1-$, $-SO_2NH-$, $-NHSO_2-$, $-NR^1SO_2-$; $-SO_2NR^1-$, $-SO_3-$ (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; $-ONR^1$; NR^1O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-, with X attached either *meta* or *para*.

Y = H, O, OR^1, NH, NR^1, S, -S-S-, *R* or *S* or racemic –S(lone pair)=O-, $-SO_2-$, -SONH-, -NHSO-, $-NR^1SO-$, $-SONR^1-$, $-SO_2NH-$, $-NHSO_2-$, $-NR^1SO_2-$; $-SO_2NR^1-$, $-SO_3-$ (sulfonate), C=O, -NHNH-, -N=N-, -NHO-, -ONH-; $-ONR^1$; NR^1O-, *E* or *Z* -CH=CH-; -C≡C-; CH_2; -C=N-, with Y attached either *meta* or *para*.

Q,L,M, V, α, and **U** are any combination of CH, S, O, N, N-oxide. For example, when **L** and **M** are both O, a furo-[2,3-*b*]furan is indicated in which the side-chains can be attached to provide the 2,3-; 2,4-; 2,5-; or 3,4-disubstituted furo-[2,3-*b*]furans. When **M** and **U** are both O, a furo-[3,2-b]furan is indicated in which the side chains can be attached to provide the 2,3-; 2,5-; 2,6-disubstituted furo-[3,2-*b*]furans. When **L** is an oxygen atom and **M** is a nitrogen atom, the resultant heterocycle is a 6*H*-furo[2,3-*b*]pyrrole, where substitution can occur at the 2,3-; 2,4-; 2,5-; and 2,6-positions.

Z = CO_2R^1; *R* or *S* or racemic 5-substituted-thiazolidine-2,4-dione; *R* or *S* or racemic 3-substituted-pyrrolidine-2,5-dione; all diastereomers of 3,4-disubstituted-pyrrolidine-2,5-dione; *R* or *S* or racemic 4-substituted-azetidine-2-one; *R* or *S* or racemic 3-substituted-azetidine-2-one; all diastereomers of 3,4-disubstituted-azetidine-2-one; 3-substituted-azetidine-2,4-dione; 1-substituted-1,3-diazetidine-2,4-dione; 1-substituted-1,3-diazetidine-2-one; all diastereomers of 1,4-disubstituted-1,3-diazetidine-2-one; 5-substituted-2,4-dihydro-[1,2,4]triazol-3-one; 4-hydroxy-5-substituted-1,2-dihydro-pyrazol-3-one; 4-alkoxy-5-substituted-1,2-dihydro-pyrazol-3-one; 4-alkoxy-substituted-1,2-dihydro-pyrazol-3-one; 5-substituted-2H-pyrazole-3,4-dione; 5-substituted-imidazole-2,4-dione; 3-substituted-pyrrole-2,5-dione; 3-Hydroxy-4-substituted-pyrrole-2,5-dione; 3-alkoxy-4-substituted-pyrrole-2,5-dione; 3-alkoxy-substituted-pyrrole-2,5-dione; 5-substituted-oxazolidine-2,4-dione; 5-substituted-imidazolidine-2,4-dione; 5-substituted-1,2-dihydro-pyrazol-3-one; 5-substituted-2H-tetrazole; 4-substituted-2H-[1,2,3]triazole; 3-substituted-1H-[1,2,4]triazole; R or S or racemic 5-substituted-3,5-dihydro-[1,2,3]triazol-4-one; 5-substituted-2,3-dihydro-[1,2,3]triazol-4-one; R or S or racemic 4-substituted-pyrazolidine-3,5-dione; 4-substituted-[1,2,4]triazolidine-3,5-dione. Also, all benzo-fused examples of the above

monocycles such as, but not limited to: 2, 3, 4 or 5-substituted-isoindole-1,3-dione; 3, 4 or 5-substituted-1,2-dihydro-indazol-3-one; 3, 4 or 5-substituted-2H-benzotriazole, and so on.

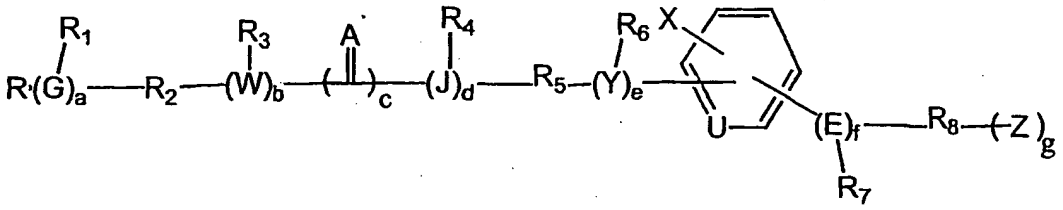
When **t** = 1, one of β or γ is either CH_2, O, N, or S and together with the other, form a cis or trans cyclopropane, epoxide, aziridine, or episulfide. Concurrently, δ and μ are either cis or trans to one another, and can be any combination of H, alkyl, cycloalkyl, aryl, heterocyclic, heteroaryl, alkylaryl, alkylcycloalkyl, alkylheterocyclic, alkylheteroaryl, and optionally substituted derivatives therein. Preferred in this arrangement is the cis-cyclopropyl compound.

When **t** = 1, together β and γ form a second bond that is either cis or trans (*E* or *Z*) such that the overall unit enclosed by **t** is a double bond. Concurrently, δ and μ are either cis or trans to one another, and can be any combination of H, alkyl, alkoxyl, halogen, thioalkoxyl, acyloxyl, cycloalkyl, aryl, heterocyclic, heteroaryl, alkylaryl, alkylcycloalkyl, alkylheterocyclic, alkylheteroaryl, and optionally substituted derivatives therein. Alternatively, together β and γ form a second bond while concurrently, δ and μ form a third bond such that the entire unit enclosed by **t** is a triple bond (alkyne). Preferred in this arrangement is the *Z*-double bond. Another example is exemplified when the Z-double bond is substituted by δ and μ such that together they form a ring. This ring can be benzenoid, heterocyclic, heteroaryl, and so on.

Other Formulas of the Invention

[0122] Compounds within the scope of the invention include the following.

[0123] Compounds of Formula 1 are provided:



where the following apply:

a = 0 to 1; **b** = 0 to 1; **c** = 0-2; **d** = 0 to 1; **e** = 0 to1; **f** = 0 to 1, **g** = 0 to 1.

A = O or S.

R, R_1 – R_{11} = independently any combination of naught (i.e. not present), H, lone pair of electrons, optionally substituted heteroatomic group, or alkyl, cycloalkyl, alkylcycloalkyl, arylalkyl, aryl, heteroaryl, heterocyclic, alkylheteroaryl, or alkylheterocyclic group; or optionally substituted ester, amide, carbonate, or carbamate.

W, G, E or **J** = independently O, N, S, $-SO_2-$,$-NHSO_2-$; $-SO_2NH-$; C, C=O, CH, or CH_2.

X = H, halogen, OR_{10}, $NR_{10}R_{11}$, SR, $-SO_2R$, $-SO_2\ NR_{10}R_{11}$, or $-NR_{10}SO_2R_{11}$, with X attached either *meta* or *para* to the Z containing side chain.

Y = O, N, S, $-SO_2-$,$-NHSO_2-$; $-SO_2NH-$; C, C=O, CH, or CH_2 with Y attached either *meta* or *para* to the Z containing side chain.

U can be CH, CX, CY, N, or N-oxide; where the point of attachment of Y and X are preferably via carbon atoms in the central ring.

Z = CO_2R_9; *R* or *S* or racemic 5-substituted-thiazolidine-2,4-dione; *R* or *S* or racemic 3-substituted-pyrrolidine-2,5-dione; 5-substituted-oxazolidine-2,4-dione; 5-substituted-imidazolidine-2,4-dione; 5-substituted-isoindole-1,3-dione; 3-substituted-pyrrole-2,4-dione; 3-Hydroxy-4-substituted-pyrrole-2,5-dione; 4-hydroxy-5-substituted-1,2-dihydropyrazol-3-one; 5-substituted-1,2-dihydro-pyrazol-3-one; 4-substituted-pyrazolidine-3,5-

dione; 3-substituted-1H-[1,2,4]triazole; 4-substituted-2H-[1,2,3]triazole; 4-substituted-[1,2,4]triazolidine-3,5-dione; 5-substituted-2,3-dihydro-[1,2,3]triazol-4-one; or 5-substituted-2H-tetrazole.

[0124] In one embodiment of Formula 1:

R_1 is a 2, 3, or 4-pyridyl ring;

R is a lone pair of electrons (lpe), H, substituted or unsubsituted alkyl or aryl group;

G = CH;

b,f = 0; a, c,d,g and e = 1;

R_2 = $-(CH_2)_6$ to $-(CH_2)_2-$;

R_4 = H, CH_3, ethyl, or propyl;

R_5 = $-(CH_2)-$ to $-(CH_2)_4-$;

R_6 = lone pair of electrons (lpe) or H, substituted or unsubsituted alkyl or aryl group;

A = O or S;

J = O, N, or S;

Y = O, N, S, or CH;

X = H, F, Cl, Br, or I;

U = N, or CH;

R_8 = CH=CH-, C=O, or CH_2;

R_9 = H, substituted or unsubstituted alkyl group, or nontoxic metal salt;

Z = $COOR_9$ or 5-substituted 1,3-thiazolidine-2,4-dione;

[0125] In one particular embodiment of Formula 1:

R_1 is a 4-pyridyl ring;

R is a lpe, H, substituted or unsubsituted alkyl group;

G = CH;

b,f = 0; a, c,d,g and e = 1;

R_2 = $-(CH_2)_6$ to $-(CH_2)_4-$;

$R_4 = CH_3$;

$R_5 = -(CH_2)_2-$ to $-(CH_2)_4-$;

R_6 = lpe or H, substituted or unsubstituted alkyl group;

A = O or S;

J = O, N, or S;

Y = O or S;

X = H, F, Cl;

U = CH;

$R_8 = CH_2$; and

Z = 5-substituted 1,3-thiazolidine-2,4-dione.

[0126] In a more particular embodiment of Formula 1:

R_1 is a 4-pyridyl ring

R = H

G = CH

b,f = 0; a, c,d,g and e = 1

$R_2 = -(CH_2)_3-$

$R_4 = CH_3$

$R_5 = -(CH_2)_2-$

R_6 = lpe

A = O

J = N

Y = O

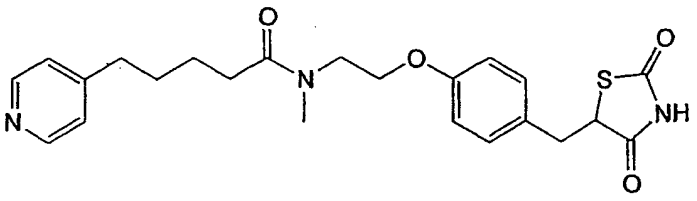
X = H

U = CH

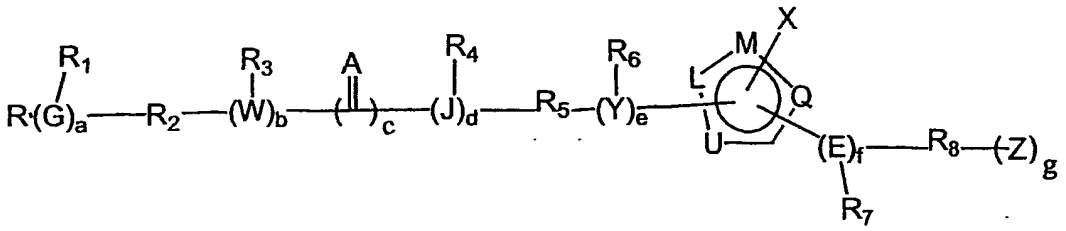
$R_8 = CH_2$ and

Z = 5-substituted 1,3-thiazolidine-2,4-dione.

In one embodiment the compound is:



[0127] Compounds also are provided of Formula 2:



Where the following apply:

a = 0,1; b = 0,1; c = 0-2; d = 0,1; e = 0,1; f = 0,1, g = 0,1.

A = O, S.

R, $R_1 - R_{11}$ = independently any combination of naught, H, lone pair of electrons, optionally substituted heteroatomic group, or alkyl, cycloalkyl, alkylcycloalkyl, arylalkyl, aryl, heteroaryl, heterocyclic, alkylheteroaryl, or alkylheterocyclic group; or optionally substituted ester, amide, carbonate, or carbamate.

W, G, E or J = independently O, N, S, $-SO_2-$,$-NHSO_2-$; $-SO_2NH-$; C, C=O, CH, or CH_2.

X = H, halogen, OR_{10}, $NR_{10}R_{11}$, SR, $-SO_2R$, $-SO_2NR_{10}R_{11}$, $-NR_{10}SO_2R_{11}$, with X attached either *meta* or *para* to the Z containing side chain.

Y = O, N, S, $-SO_2-$,$-NHSO_2-$; $-SO_2NH-$; C, C=O, CH, CH_2 with Y attached either *meta* or *para* to the Z containing side chain.

U, L, M, Q can independently be CH, CX, CY, S, N, N-oxide.

Z = CO_2R_9; *R* or *S* or racemic 5-substituted-thiazolidine-2,4-dione; *R* or *S* or racemic 3-substituted-pyrrolidine-2,5-dione; 5-substituted-oxazolidine-2,4-dione; 5-substituted-imidazolidine-2,4-dione; 5-substituted-isoindole-

1,3-dione; 3-substituted-pyrrole-2,4-dione; 3-Hydroxy-4-substituted-pyrrole-2,5-dione; 4-hydroxy-5-substituted-1,2-dihydropyrazol-3-one; 5-substituted-1,2-dihydro-pyrazol-3-one; 4-substituted-pyrazolidine-3,5-dione; 3-substituted-1H-[1,2,4]triazole; 4-substituted-2H-[1,2,3]triazole; 4-substituted-[1,2,4]triazolidine-3,5-dione; 5-substituted-2,3-dihydro-[1,2,3]triazol-4-one; 5-substituted-2H-tetrazole.

[0128] In one embodiment of Formula 2:

R_1 is a *N*-methylated 2, 3, or 4-piperidenyl ring.

R is a lpe, H, substituted or unsubsituted alkyl or aryl group.

G = CH

b,f = 0; a, c,d,g and e = 1

R_2 = $-(CH_2)_6$ to $-(CH_2)_2-$

R_4 = H, CH_3, ethyl, propyl

R_5 = $-(CH_2)-$ to $-(CH_2)_4-$

R_6 = lpe or H, substituted or unsubsituted alkyl or aryl group.

A = O or S

J = O, N, or S

Y = O, N, S, or CH

X = H, F, Cl, Br, or I

U, L, M, Q = independently CH or C, N, NH, O, S

R_8 = CH=CH- or CH_2

R_9 = H, substituted or unsubstituted alkyl group, or nontoxic metal salt.

Z = $COOR_9$ or 5-substituted 1,3-thiazolidine-2,4-dione

[0129] In one particular embodiment of Formula 2:

R_1 is a 4-N-methyl piperidenyl ring.

R is a lpe, H, substituted or unsubstituted alkyl group.

G = CH

b,f = 0; a, c,d,g and e = 1

R_2 = -$(CH_2)_6$ to -$(CH_2)_3$-

$R_4 = CH_3$

R_5 = -(CH_2)- to -$(CH_2)_4$-

R_6 = lpe or H, substituted or unsubsituted alkyl group.

A = O or S

J = O, N, or S

Y = O, N, or CH

X = H, F, Cl

U, L, M, Q = independently CH or C, N, NH, or O

$R_8 = CH_2$

Z = 5-substituted 1,3-thiazolidine-2,4-dione

[0130] In a more particular embodiment of Formula 2:

R_1 is a 4-pyridyl ring.

R = H

G = CH

b,f = 0; a,c,d,g and e = 1

R_2 = -$(CH_2)_4$-

$R_4 = CH_3$

R_5 = -$(CH_2)_2$-

R_6 = H

A = O

J = N

U = O, M, Q = H; L = C

Y = CH

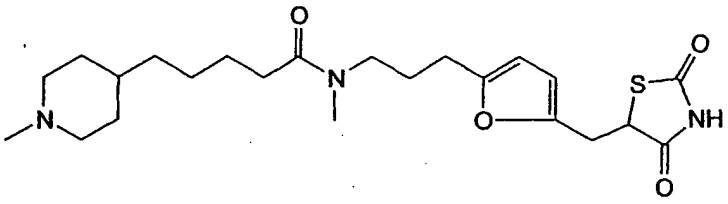
X = H

$R_8 = CH_2$

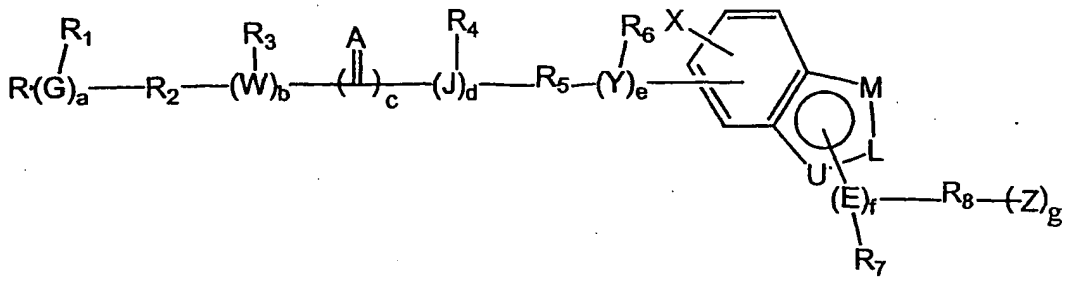
Z = 5-substituted 1,3-thiazolidine-2,4-dione

and R_8 and Y are attached 2,5 to one another on the ring.

In one embodiment the compound is:



[0131] Compounds also are provided of Formula 3:



Where the following apply:

a = 0,1; b = 0,1; c = 0-2; d = 0,1; e = 0,1; f = 0,1, g = 0,1.

A = O, S.

R, $R_1 - R_{11}$ = independently any combination of naught, H, lone pair of electrons, optionally substituted heteroatomic group, or alkyl, cycloalkyl, alkylcycloalkyl, arylalkyl, aryl, heteroaryl, heterocyclic, alkylheteroaryl, or alkylheterocyclic group; or optionally substituted ester, amide, carbonate, or carbamate.

W, G, E or J = independently O, N, S, $-SO_2-$,$-NHSO_2-$; $-SO_2NH-$; C, C=O, CH, CH_2.

X = H, halogen, OR_{10}, $NR_{10}R_{11}$, SR, $-SO_2R$, $-SO_2 NR_{10}R_{11}$, $-NR_{10}SO_2R_{11}$, with X attached either *meta* or *para* to the Z containing side chain.

Y = O, N, S, $-SO_2-$,$-NHSO_2-$; $-SO_2NH-$; C, C=O, CH, CH_2 with Y attached either *meta* or *para* to the Z containing side chain.

U, L, or M can independently be CH, N, NH, S, O, C=O; where the point of attachment of Y and X are preferably via carbon atoms in the benzo ring.

Z = CO_2R_9; *R* or *S* or racemic 5-substituted-thiazolidine-2,4-dione; *R* or *S* or racemic 3-substituted-pyrrolidine-2,5-dione; 5-substituted-oxazolidine-2,4-dione; 5-substituted-imidazolidine-2,4-dione; 5-substituted-isoindole-1,3-dione; 3-substituted-pyrrole-2,4-dione; 3-Hydroxy-4-substituted-pyrrole-2,5-dione; 4-hydroxy-5-substituted-1,2-dihydropyrazol-3-one; 5-substituted-1,2-dihydro-pyrazol-3-one; 4-substituted-pyrazolidine-3,5-dione; 3-substituted-1H-[1,2,4]triazole; 4-substituted-2H-[1,2,3]triazole; 4-substituted-[1,2,4]triazolidine-3,5-dione; 5-substituted-2,3-dihydro-[1,2,3]triazol-4-one; 5-substituted-2H-tetrazole.

[0132] In one embodiment of Formula 3:

R_1 is a SH, SAc, or SMe.

R is a lpe, H, substituted or unsubsituted alkyl or aryl group.

G = CH

b,f = 0; a, c,d,g and e = 1

R_2 = $-(CH_2)_{10}$ to $-(CH_2)_4-$

R_4 = H, CH_3, ethyl, propyl

R_5 = $-(CH_2)$ - to $-(CH_2)_4-$

R_6 = lpe or H, substituted or unsubsituted alkyl or aryl group.

A = O or S

J = O, N, CH or S

Y = O, N, CH or S

X = H, F, Cl, Br, or I

U, L, M = N, NH, C, CH, S

R_8 = CH=CH- or CH_2

R_9 = H, substituted or unsubstituted alkyl group, or nontoxic metal salt.

Z = $COOR_9$ or 5-substituted 1,3-thiazolidine-2,4-dione.

[0133] In one particular embodiment of Formula 3:

R_1 is a SAc group

R is a lpe, H, substituted or unsubsituted alkyl group

G = CH

b,f = 0; a, c,d,g and e = 1

R_2 = $-(CH_2)_8$ to $-(CH_2)_6-$

$R_4 = CH_3$

R_5 = $-(CH_2)$ - to $-(CH_2)_4-$

R_6 = lpe or H, substituted or unsubsituted alkyl group.

A = O or S

J = O, N, or S

Y = O, N, or S

X = H, F, Cl, Br, or I

U, L, M = CH, C, NH

$R_8 = CH_2$

Z = 5-substituted 1,3-thiazolidine-2,4-dione

[0134] In a more particular embodiment of Formula 3:

R_1 is a SAc group

R = H

G = CH

b,f, e= 0; a, c,d,g = 1

R_2 = $-(CH_2)_6-$

$R_4 = CH_3$

R_5 = $-(CH_2)-$

A = O

J = N

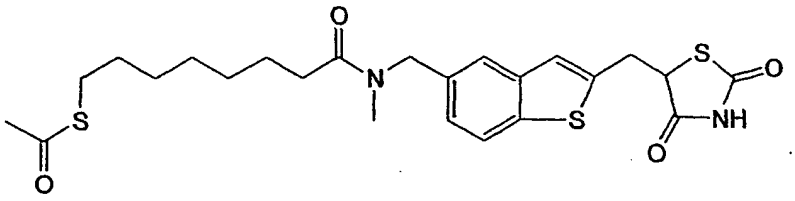
X = H

U = S; L = C; M = CH

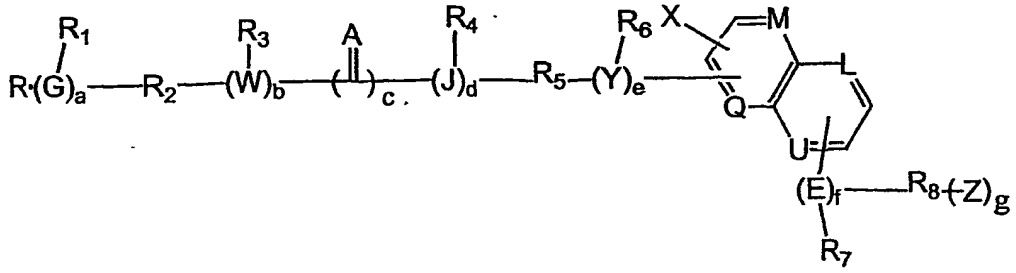
$R_8 = CH_2$

Z = 5-substituted 1,3-thiazolidine-2,4-dione.

In one embodiment the compound is



[0135] Provided are compounds of Formula 4:



Where the following apply:

a = 0,1; b = 0,1; c = 0-2; d = 0,1; e = 0,1; f = 0,1, g = 0,1.

A = O, S.

R, $R_1 - R_{11}$ = independently any combination of naught, H, lone pair of electrons, optionally substituted heteroatomic group, or alkyl, cycloalkyl, alkylcycloalkyl, arylalkyl, aryl, heteroaryl, heterocyclic, alkylheteroaryl, or alkylheterocyclic group; or optionally substituted ester, amide, carbonate, or carbamate.

W, G, E or J = independently O, N, S, $-SO_2-$,$-NHSO_2-$; $-SO_2NH-$; C, C=O, CH, CH_2.

X = H, halogen, OR_{10}, $NR_{10}R_{11}$, SR, $-SO_2R$, $-SO_2\ NR_{10}R_{11}$, $-NR_{10}SO_2R_{11}$, with X attached either *meta* or *para* to the Z containing side chain.

Y = O, N, S, $-SO_2-$,$-NHSO_2-$; $-SO_2NH-$; C, C=O, CH, CH_2 with Y attached either *meta* or *para* to the Z containing side chain.

U, L, Q, M can independently be CH, CX, CY, N, or N-oxide; where the point of attachment of Y and X are preferably via carbon atoms in the central ring.

Z = CO_2R_9; *R* or *S* or racemic 5-substituted-thiazolidine-2,4-dione; *R* or *S* or racemic 3-substituted-pyrrolidine-2,5-dione; 5-substituted-oxazolidine-2,4-dione; 5-substituted-imidazolidine-2,4-dione; 5-substituted-isoindole-1,3-dione; 3-substituted-pyrrole-2,4-dione; 3-Hydroxy-4-substituted-pyrrole-2,5-dione; 4-hydroxy-5-substituted-1,2-dihydropyrazol-3-one; 5-substituted-1,2-dihydro-pyrazol-3-one; 4-substituted-pyrazolidine-3,5-dione; 3-substituted-1H-[1,2,4]triazole; 4-substituted-2H-[1,2,3]triazole; 4-substituted-[1,2,4]triazolidine-3,5-dione; 5-substituted-2,3-dihydro-[1,2,3]triazol-4-one; or 5-substituted-2H-tetrazole.

[0136] In one embodiment of Formula 4:

R_1 is a 2, 3, or 4-Cl benzene ring

R is a lpe, H, substituted or unsubsituted alkyl or aryl group

G = CH, N

b,f = 0; a, c,d,g and e = 1

R_2 = $-(CH_2)_6$ to $-(CH_2)_2-$

R_4 = H, CH_3, ethyl, propyl

R_5 = $-(CH_2)-$ to $-(CH_2)_4-$

R_6 = lpe or H, substituted or unsubsituted alkyl or aryl group.

A = O or S

J = O, N, CH or S

Y = O, N, S, or CH

X = H, F, Cl, Br, or I

U, L, Q, M can be CH, CX, CY, N, N-oxide

R_8 = CH=CH-, C=O, or CH_2

R_9 = H, substituted or unsubstituted alkyl group, or nontoxic metal salt, and

Z = $COOR_9$ or 5-substituted 1,3-thiazolidine-2,4-dione.

[0137] In one particular embodiment of Formula 4:

R_1 is a 4-pyridyl ring

R is a lpe, H, substituted or unsubsituted alkyl group

G = CH, N

b,f = 0; a, c,d,g and e = 1

R_2 = $-(CH_2)_6$ to $-(CH_2)_4-$

$R_4 = CH_3$

R_5 = $-(CH_2)_2-$ to $-(CH_2)_4-$

R_6 = lpe or H, substituted or unsubsituted alkyl group.

A = O or S

J = O, N, or S

Y = O or S

X = H, F, Cl

U, L, Q, M can be CH, CX, CY, N

$R_8 = CH_2$

Z = 5-substituted 1,3-thiazolidine-2,4-dione.

[0138] In a more particular embodiment of Formula 4:

R_1 is a 4-Cl benzene ring.

R = H

G = CH

b,f,e = 0; a, c,d,g = 1

R_2 = $-(CH_2)_3-$

$R_4 = CH_3$

R_5 = $-(CH_2)-$

A = O

J = N

X = H

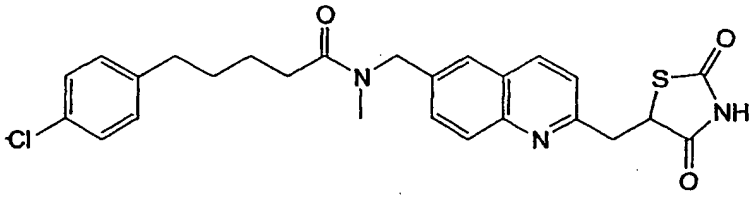
U = N; L, Q, M are CH

$R_8 = CH_2$

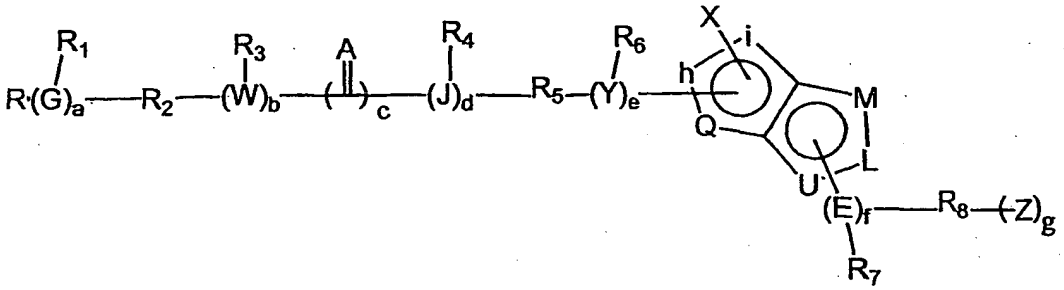
Z = 5-substituted 1,3-thiazolidine-2,4-dione

where R_8 and R_5 are on the 2,6 positions of a quinoline ring.

In one embodiment the compound is:



[0139] Compounds also are provided of Formula 5:



Where the following apply:

a = 0,1; b = 0,1; c = 0-2; d = 0,1; e = 0,1; f = 0,1, g = 0,1.

A = O, S.

R, $R_1 - R_{11}$ = independently any combination of naught, H, lone pair of electrons, optionally substituted heteroatomic group, or alkyl, cycloalkyl, alkylcycloalkyl, arylalkyl, aryl, heteroaryl, heterocyclic, alkylheteroaryl, or alkylheterocyclic group; or optionally substituted ester, amide, carbonate, or carbamate.

W, G, E or J = independently O, N, S, $-SO_2-$,$-NHSO_2-$; $-SO_2NH-$; C, C=O, CH, CH_2.

X = H, halogen, OR_{10}, $NR_{10}R_{11}$, SR, $-SO_2R$, $-SO_2NR_{10}R_{11}$, $-NR_{10}SO_2R_{11}$.

Y = O, N, S, $-SO_2-$,$-NHSO_2-$; $-SO_2NH-$; C, C=O, CH, CH_2.

U, L, Q, h, i or M can be independently CH, N, NH, S, O, C=O.

Z = CO_2R_9; *R* or *S* or racemic 5-substituted-thiazolidine-2,4-dione; *R* or *S* or racemic 3-substituted-pyrrolidine-2,5-dione; 5-substituted-oxazolidine-2,4-dione; 5-substituted-imidazolidine-2,4-dione; 5-substituted-isoindole-1,3-dione; 3-substituted-pyrrole-2,4-dione; 3-Hydroxy-4-substituted-pyrrole-2,5-dione; 4-hydroxy-5-substituted-1,2-dihydropyrazol-3-one; 5-substituted-1,2-dihydro-pyrazol-3-one; 4-substituted-pyrazolidine-3,5-dione; 3-substituted-1H-[1,2,4]triazole; 4-substituted-2H-[1,2,3]triazole; 4-substituted-[1,2,4]triazolidine-3,5-dione; 5-substituted-2,3-dihydro-[1,2,3]triazol-4-one; 5-substituted-2H-tetrazole.

[0140] In one embodiment of Formula 5:

R_1 is a SH, SAc, S-aminoacid, or Salkyl.

R is a lpe, H, substituted or unsubsituted alkyl or aryl group.

e,b,f = 0; c,d,g and a = 1

G = CH, N

R_2 = $-(CH_2)_{10}$ to $-(CH_2)_4-$

R_4 = H, CH_3, ethyl, propyl

R_5 = $-(CH_2)$ - to $-(CH_2)_4-$

R_6 = lpe or H, substituted or unsubsituted alkyl or aryl group.

A = O or S

J = O, N, or S

Y = O, N, or S

X = H, F, Cl, Br, or I

U, L, M, Q, h, i independently = N, NH, C, CH, S, or O

R_8 = CH=CH- or CH_2

R_9 = H, substituted or unsubstituted alkyl group, or nontoxic metal salt

Z = $COOR_9$ or 5-substituted 1,3-thiazolidine-2,4-dione.

[0141] In one particular embodiment of Formula 5:

R_1 is a Sglycinate salt group.

a,b,f = 0; c,d,g and e = 1

R is a lpe, H, substituted or unsubsituted alkyl group.

R_2 = $-(CH_2)_8$ to $-(CH_2)_6-$

$R_4 = CH_3$

R_5 = $-(CH_2)$ - to $-(CH_2)_4-$

R_6 = lpe or H, substituted or unsubsituted alkyl group.

A = O or S

G = CH, N

J = O, N, or S

Y = O, N, or S

X = H, F, Cl, Br, or I

U, L, M, Q, h, and i independently = CH, C, N, O, S

$R_8 = CH_2$

Z = 5-substituted 1,3-thiazolidine-2,4-dione.

[0142] In a more particular embodiment of Formula 5:

R_1 is a Sglycinate salt group.

a,b,f = 0; c,d,g and e = 1

R is a H.

R_2 = $-(CH_2)_7-$

$R_4 = CH_3$

R_5 = $-(CH_2)$ -

A = O

G = CH

J = N

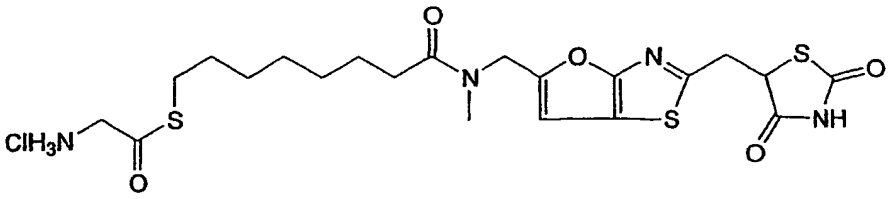
X = H

U = S; L = CH; M = N, Q = CH; h = C; i = O

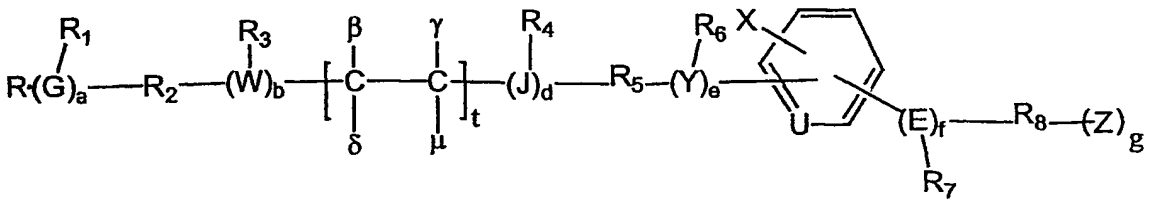
$R_8 = CH_2$

Z = 5-substituted 1,3-thiazolidine-2,4-dione.

[0143] In one embodiment the compound is:



[0144] Compounds are provided of Formula 6:



Where the following apply:

a = 0,1; b = 0,1; t = 0-2; d = 0,1; e = 0,1; f = 0,1, g = 0,1.

R, $R_1 - R_{11}$ = independently any combination of naught, H, lone pair of electrons, optionally substituted heteroatomic group, or alkyl, cycloalkyl, alkylcycloalkyl, arylalkyl, aryl, heteroaryl, heterocyclic, alkylheteroaryl, or alkylheterocyclic group; or optionally substituted ester, amide, carbonate, or carbamate.

W, G, E or J = independently O, N, S, $-SO_2-$,$-NHSO_2-$; $-SO_2NH-$; C, C=O, CH, CH_2.

X = H, halogen, OR_{10}, $NR_{10}R_{11}$, SR, $-SO_2R$, $-SO_2 NR_{10}R_{11}$, $-NR_{10}SO_2R_{11}$, with X attached either *meta* or *para* to the Z containing side chain.

Y = O, N, S, $-SO_2-$,$-NHSO_2-$; $-SO_2NH-$; C, C=O, CH, CH_2 with Y attached either *meta* or *para* to the Z containing side chain.

U can be CH, CX, CY, N, N-oxide; where the point of attachment of Y and X are preferably via carbon atoms in the central ring.

Z = CO_2R_9; *R* or *S* or racemic 5-substituted-thiazolidine-2,4-dione; *R* or *S* or racemic 3-substituted-pyrrolidine-2,5-dione; 5-substituted-oxazolidine-2,4-dione; 5-substituted-imidazolidine-2,4-dione; 5-substituted-isoindole-1,3-dione; 3-substituted-pyrrole-2,4-dione; 3-Hydroxy-4-substituted-pyrrole-2,5-dione; 4-hydroxy-5-substituted-1,2-dihydropyrazol-3-one; 5-substituted-1,2-dihydro-pyrazol-3-one; 4-substituted-pyrazolidine-3,5-dione; 3-substituted-1H-[1,2,4]triazole; 4-substituted-2H-[1,2,3]triazole; 4-substituted-[1,2,4]triazolidine-3,5-dione; 5-substituted-2,3-dihydro-[1,2,3]triazol-4-one; 5-substituted-2H-tetrazole.

When t = 1, one of β or γ is either CH_2, O, N, or S and together with the other, form a cis or trans cyclopropane, epoxide, aziridine, or episulfide. Concurrently, δ and μ are either cis or trans to one another, and can be any combination of H, alkyl, cycloalkyl, aryl, heterocyclic, heteroaryl, alkylaryl, alkylcycloalkyl, alkylheterocyclic, alkylheteroaryl, and optionally substituted derivatives therein.

When t = 1, together β and γ form a second bond that is either cis or trans (*E* or *Z*) such that the overall unit enclosed by t is a double bond. Concurrently, δ and μ are either cis or trans to one another, and can be any combination of H, alkyl, alkoxyl, halogen, thioalkoxyl, acyloxyl, cycloalkyl, aryl, heterocyclic, heteroaryl, alkylaryl, alkylcycloalkyl, alkylheterocyclic, alkylheteroaryl, and optionally substituted derivatives therein. Alternatively, together β and γ form a second bond while concurrently, δ and μ form a third bond such that the entire unit enclosed by t is a triple bond (alkyne).

[0145] In one embodiment of Formula 6:

R_1 is a 2, 3, or 4-pyridyl ring.

R is a lpe, H, substituted or unsubsituted alkyl or aryl group.

a,d, f ,g, t and e = 1; b = 0

R_2 = -$(CH_2)_6$ to -$(CH_2)_2$-

R_5 = -$(CH_2)_4$- to -(CH_2)-

R_6 = lpe or H, substituted or unsubsituted alkyl or aryl group.

E, G, J, Y, W = independently O, N, S, C=O, CH, CH_2

X = H, F, Cl, Br, or I

U = N, CH

β or γ is either CH_2, O, N, or S and together with the other, form a cis or trans cyclopropane, double bond, epoxide, aziridine, or episulfide.

When both β or γ and δ or μ are double bonds, a triple bond results.

R_8 = CH=CH- or CH_2

R_9 = H, substituted or unsubstituted alkyl group, or nontoxic metal salt.

Z = $COOR_9$ or 5-substituted 1,3-thiazolidine-2,4-dione.

[0146] In one particular embodiment of Formula 6:

R_1 is a 3-pyridyl ring.

R is H

G is CH

b,d,f = 0; a,g, t and e = 1

R_2 = -$(CH_2)_6$ to -$(CH_2)_4$-

R_5 = -$(CH_2)_2$- to -$(CH_2)_4$-

R_6 is a lpe, H, substituted or unsubsituted alkyl group.

Y = O, N, or S

X = H, F, or Cl.

U = CH

β or γ is either CH_2, and together with the other, form a cis or trans cyclopropane or double bond.

When both β or γ and δ or μ are double bonds, a triple bond results.

R_8 = *E* or *Z* -CH=CH-

R_9 = a variously substituted alkyl group.

Z = $COOR_9$ or 5-substituted 1,3-thiazolidine-2,4-dione.

[0147] In a more particular embodiment of Formula 6:

R_1 is a 3-pyridyl ring.

R is H

G is CH

b,d,f = 0; a,g, t and e = 1

R_2 = $-(CH_2)_3-$

R_5 = $-(CH_2)_2-$

R_6 = Ipe

Y = O

X = F

U = CH

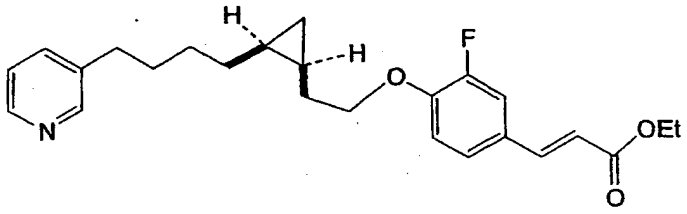
β or γ is a CH_2, and together with the other, form a cis or trans cyclopropane.

R_8 = *E* or *Z* -CH=CH-

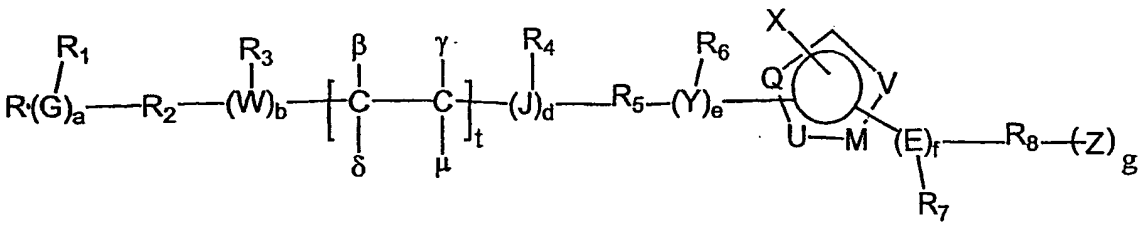
Z = $COOR_9$

R_9 = ethyl.

In one embodiment the compound is:



[0148] In one embodiment, compounds are provided of Formula 7:



Where the following apply:

a = 0,1; b = 0,1; t = 0-2; d = 0,1; e = 0,1; f = 0,1, g = 0,1.

R, $R_1 - R_{11}$ = independently any combination of naught, H, lone pair of electrons, optionally substituted heteroatomic group, or alkyl, cycloalkyl, alkylcycloalkyl, arylalkyl, aryl, heteroaryl, heterocyclic, alkylheteroaryl, or alkylheterocyclic group; or optionally substituted ester, amide, carbonate, or carbamate.

W, G, E or J = independently O, N, S, $-SO_2-$,$-NHSO_2-$; $-SO_2NH-$; C, C=O, CH, CH_2.

X = H, halogen, OR_{10}, $NR_{10}R_{11}$, SR, $-SO_2R$, $-SO_2\ NR_{10}R_{11}$, $-NR_{10}SO_2R_{11}$.

Y = O, N, S, $-SO_2-$,$-NHSO_2-$; $-SO_2NH-$; C, C=O, CH, CH_2.

U, V, M, Q independently can be C, CH, CX, S, N, NH, O.

Z = CO_2R^1; *R* or *S* or racemic 5-substituted-thiazolidine-2,4-dione; *R* or *S* or racemic 3-substituted-pyrrolidine-2,5-dione; 5-substituted-oxazolidine-2,4-dione; 5-substituted-imidazolidine-2,4-dione; 5-substituted-isoindole-1,3-dione; 3-substituted-pyrrole-2,4-dione; 3-Hydroxy-4-substituted-pyrrole-2,5-dione; 4-hydroxy-5-substituted-1,2-dihydropyrazol-3-one; 5-substituted-1,2-dihydro-pyrazol-3-one; 4-substituted-pyrazolidine-3,5-dione; 3-substituted-1H-[1,2,4]triazole; 4-substituted-2H-[1,2,3]triazole; 4-substituted-[1,2,4]triazolidine-3,5-dione; 5-substituted-2,3-dihydro-[1,2,3]triazol-4-one; 5-substituted-2H-tetrazole.

When t = 1, one of β or γ is either CH_2, O, N, or S and together with the other, form a cis or trans cyclopropane, epoxide, aziridine, or episulfide.

Concurrently, δ and μ are either cis or trans to one another, and can be any combination of H, alkyl, cycloalkyl, aryl, heterocyclic, heteroaryl, alkylaryl, alkylcycloalkyl, alkylheterocyclic, alkylheteroaryl, and optionally substituted derivatives therein.

When t = 1, together β and γ form a second bond that is either cis or trans (*E* or *Z*) such that the overall unit enclosed by t is a double bond.

Concurrently, δ and μ are either cis or trans to one another, and can be any combination of H, alkyl, alkoxyl, halogen, thioalkoxyl, acyloxyl, cycloalkyl, aryl, heterocyclic, heteroaryl, alkylaryl, alkylcycloalkyl, alkylheterocyclic, alkylheteroaryl, and optionally substituted derivatives therein. Alternatively, together β and γ form a second bond while concurrently, δ and μ form a third bond such that the entire unit enclosed by t is a triple bond (alkyne).

[0149] In one embodiment of Formula 7:

R_1 is a 2, 3, or 4-*N*-methylpiperidinyl ring

R is a lpe, H, substituted or unsubstituted alkyl or aryl group

a,b,d, f ,g, t and e = 1

R_2 = $-(CH_2)_6$ to $-(CH_2)_2-$

R_3 = H, lpe, substituted or unsubsituted alkyl or aryl group

R_4 = H, lpe, substituted or unsubsituted alkyl or aryl group

R_5 = $-(CH_2)_4-$ to $-(CH_2)-$

R_6 is a lpe, H, substituted or unsubsituted alkyl or aryl group

R_7 = H, lpe, substituted or unsubsituted alkyl or aryl group

E, G, J, Y, W = independently O, N, S, C=O, CH, or CH_2

X = H, F, or Cl

U = N or CH

β or γ is either CH_2, O, N, or S and together with the other, form a cis or trans cyclopropane, double bond, epoxide, aziridine, or episulfide

when both β or γ and δ or μ are double bonds, a triple bond results,

R_8 = CH=CH-; C=O; or CH_2

R_9 = H, substituted or unsubstituted alkyl group, or nontoxic metal salt

Z = $COOR_9$ or 5-substituted 1,3-thiazolidine-2,4-dione, 5-substituted-2H-tetrazole.

[0150] In one particular embodiment of Formula 7:

R_1 is a 4-N-methylpiperidinyl ring.

R is H

G is CH

b,d,f = 0; a,g, t and e = 1

R_2 = $-(CH_2)_4$ to $-(CH_2)_2-$

R_5 = $-(CH_2)_2-$ to $-(CH_2)_4-$

R_6 = lpe

Y = O or S

X = H, F, Cl.

U = CH

β or γ is either CH_2, and together with the other, form a cis or trans cyclopropane or double bond.

When both β or γ and δ or μ are double bonds, a triple bond results.

R_8 = C=O

Z = 5-substituted 1,3-thiazolidine-2,4-dione, 5-substituted-2H-tetrazole

[0151] In a more particular embodiment of Formula 7:

R_1 is a 4-N-methylpiperidinyl ring.

R is H

G is CH

b,d,f = 0; a,g, t and e = 1

R_2 = $-(CH_2)_3-$

R_5 = $-(CH_2)_2-$

$R_6 = H$

$Y = CH$

$X = H$

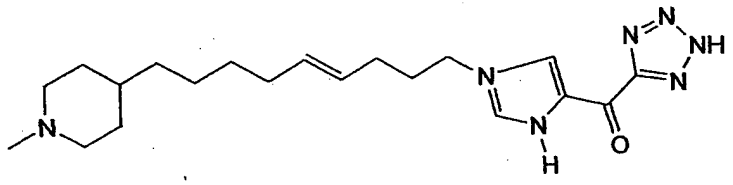
$U = CH$, $M = NH$, $Q = N$, $V = C$

β or γ is a CH_2, and together with the other, form a trans double bond.

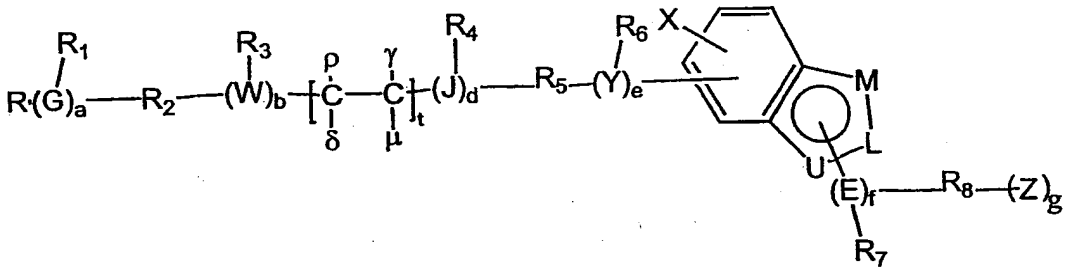
$R_8 = C{=}O$

Z = 5-substituted-2H-tetrazole.

In one embodiment the compound is:



[0152] Provided are compounds of Formula 8:



Where the following apply:

$a = 0,1$; $b = 0,1$; $t = 0\text{-}2$; $d = 0,1$; $e = 0,1$; $f = 0,1$, $g = 0,1$.

R, $R_1 - R_{11}$ = independently any combination of naught, H, lone pair of electrons, optionally substituted heteroatomic group, or alkyl, cycloalkyl, alkylcycloalkyl, arylalkyl, aryl, heteroaryl, heterocyclic, alkylheteroaryl, or alkylheterocyclic group; or optionally substituted ester, amide, carbonate, or carbamate.

W, G, E or J = independently O, N, S, $-SO_2-$,$-NHSO_2-$; $-SO_2NH-$; C, $C{=}O$, CH, CH_2.

X = H, halogen, OR_{10}, $NR_{10}R_{11}$, SR, $-SO_2R$, $-SO_2\,NR_{10}R_{11}$, $-NR_{10}SO_2R_{11}$.

Y = O, N, S, $-SO_2-$,$-NHSO_2-$; $-SO_2NH-$; C, C=O, CH, CH_2.

U, L, M independently can be C, CH, CX, S, N, NH, or O.

Z = CO_2R^1; *R* or *S* or racemic 5-substituted-thiazolidine-2,4-dione; *R* or *S* or racemic 3-substituted-pyrrolidine-2,5-dione; 5-substituted-oxazolidine-2,4-dione; 5-substituted-imidazolidine-2,4-dione; 5-substituted-isoindole-1,3-dione; 3-substituted-pyrrole-2,4-dione; 3-Hydroxy-4-substituted-pyrrole-2,5-dione; 4-hydroxy-5-substituted-1,2-dihydropyrazol-3-one; 5-substituted-1,2-dihydro-pyrazol-3-one; 4-substituted-pyrazolidine-3,5-dione; 3-substituted-1H-[1,2,4]triazole; 4-substituted-2H-[1,2,3]triazole; 4-substituted-[1,2,4]triazolidine-3,5-dione; 5-substituted-2,3-dihydro-[1,2,3]triazol-4-one; 5-substituted-2H-tetrazole.

When t = 1, one of β or γ is either CH_2, O, N, or S and together with the other, form a cis or trans cyclopropane, epoxide, aziridine, or episulfide. Concurrently, δ and μ are either cis or trans to one another, and can be any combination of H, alkyl, cycloalkyl, aryl, heterocyclic, heteroaryl, alkylaryl, alkylcycloalkyl, alkylheterocyclic, alkylheteroaryl, and optionally substituted derivatives therein.

When t = 1, together β and γ form a second bond that is either cis or trans (*E* or *Z*) such that the overall unit enclosed by t is a double bond. Concurrently, δ and μ are either cis or trans to one another, and can be any combination of H, alkyl, alkoxyl, halogen, thioalkoxyl, acyloxyl, cycloalkyl, aryl, heterocyclic, heteroaryl, alkylaryl, alkylcycloalkyl, alkylheterocyclic, alkylheteroaryl, and optionally substituted derivatives therein. Alternatively, together β and γ form a second bond while concurrently, δ and μ form a third bond such that the entire unit enclosed by t is a triple bond (alkyne).

[0153] In one embodiment of Formula 8:

R_1 is an optionally substituted alkyl group.

R is a lpe, H, substituted or unsubsituted alkyl or aryl group.

a,b,d, f ,g, t and e = 1

R_2 = -$(CH_2)_8$ to -$(CH_2)_2$-

R_3 = H, lpe, substituted or unsubsituted alkyl or aryl group.

R_4 = H, lpe, substituted or unsubsituted alkyl or aryl group.

R_5 = -$(CH_2)_4$- to -(CH_2)-

R_6 is a lpe, H, substituted or unsubsituted alkyl or aryl group.

R_7 = H, lpe, substituted or unsubsituted alkyl or aryl group.

E, G, J, Y, W = independently O, N, S, C=O, CH, CH_2

X = H, F, or Cl

U, L, M can be C, CH, CX, S, N, NH, O.

β or γ is either CH_2, O, N, or S and together with the other, form a cis or trans cyclopropane, double bond, epoxide, aziridine, or episulfide.

When both β or γ and δ or μ are double bonds, a triple bond results.

R_8 = CH=CH-; C=O; CH_2

R_9 = H, substituted or unsubstituted alkyl group, or nontoxic metal salt.

Z = $COOR_9$ or 5-substituted 1,3-thiazolidine-2,4-dione, 5-substituted-2H-tetrazole; 3-substituted-pyrrole-2,5-dione.

[0154] In one particular embodiment of Formula 8:

R_1 is a 4-N-methylpiperidinyl ring

R is H

G is CH

b,d,f = 0; a,g, t and e = 1

R_2 = -$(CH_2)_8$ to -$(CH_2)_2$-

R_5 = -$(CH_2)_2$- to -$(CH_2)_4$-

R_6 is a lpe, H, substituted or unsubsituted alkyl group.

Y = O or S

X = H, F, or Cl

U = CH

β or γ is either CH_2, and together with the other, form a cis or trans cyclopropane or double bond.

When both β or γ and δ or μ are double bonds, a triple bond results.

R_8 = C=O

Z = 5-substituted 1,3-thiazolidine-2,4-dione, 5-substituted-2H-tetrazole.

[0155] In a more particular embodiment of Formula 8:

R_1 is a thioglycinate HCl salt.

R is lpe

G is S

b,d,f,e = 0; a,g, t = 1

R_2 = $-(CH_2)_7-$

R_5 = $-(CH_2)-$

X = H

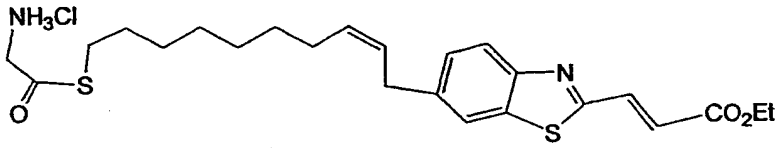
U = S, L = C; M = N

β or γ together with the other, form a cis double bond.

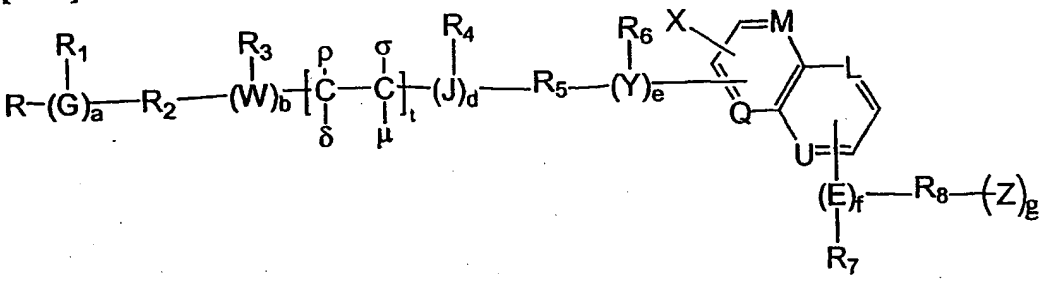
R_8 = trans -CH=CH-

Z = CO_2Et.

In one embodiment the compound is:



[0156] Formula 9 represents compounds of the formula:



Where the following apply:

a = 0,1; b = 0,1; t = 0-2; d = 0,1; e = 0,1; f = 0,1, g = 0,1.

R, $R_1 - R_{11}$ = independently any combination of naught, H, lone pair of electrons, optionally substituted heteroatomic group, or alkyl, cycloalkyl, alkylcycloalkyl, arylalkyl, aryl, heteroaryl, heterocyclic, alkylheteroaryl, or alkylheterocyclic group; or optionally substituted ester, amide, carbonate, or carbamate.

W, G, E or J = independently O, N, S, $-SO_2-$,$-NHSO_2-$; $-SO_2NH-$; C, C=O, CH, or CH_2.

X = H, halogen, OR_{10}, $NR_{10}R_{11}$, SR, $-SO_2R$, $-SO_2 NR_{10}R_{11}$, or $-NR_{10}SO_2R_{11}$.

Y = O, N, S, $-SO_2-$,$-NHSO_2-$; $-SO_2NH-$; C, C=O, CH, CH_2.

U, L, M and Q can independently be C, CH, CX, S, N, NH, O.

Z = CO_2R^1; *R* or *S* or racemic 5-substituted-thiazolidine-2,4-dione; *R* or *S* or racemic 3-substituted-pyrrolidine-2,5-dione; 5-substituted-oxazolidine-2,4-dione; 5-substituted-imidazolidine-2,4-dione; 5-substituted-isoindole-1,3-dione; 3-substituted-pyrrole-2,4-dione; 3-Hydroxy-4-substituted-pyrrole-2,5-dione; 4-hydroxy-5-substituted-1,2-dihydropyrazol-3-one; 5-substituted-1,2-dihydro-pyrazol-3-one; 4-substituted-pyrazolidine-3,5-dione; 3-substituted-1H-[1,2,4]triazole; 4-substituted-2H-[1,2,3]triazole; 4-substituted-[1,2,4]triazolidine-3,5-dione; 5-substituted-2,3-dihydro-[1,2,3]triazol-4-one; 5-substituted-2H-tetrazole.

When t = 1, one of β or γ is either CH_2, O, N, or S and together with the other, form a cis or trans cyclopropane, epoxide, aziridine, or episulfide. Concurrently, δ and μ are either cis or trans to one another, and can be any combination of H, alkyl, cycloalkyl, aryl, heterocyclic, heteroaryl, alkylaryl, alkylcycloalkyl, alkylheterocyclic, alkylheteroaryl, and optionally substituted derivatives therein.

When t = 1, together β and γ form a second bond that is either cis or trans (*E* or *Z*) such that the overall unit enclosed by t is a double bond. Concurrently, δ and μ are either cis or trans to one another, and can be any combination of H, alkyl, alkoxyl, halogen, thioalkoxyl, acyloxyl, cycloalkyl, aryl, heterocyclic, heteroaryl, alkylaryl, alkylcycloalkyl, alkylheterocyclic, alkylheteroaryl, and optionally substituted derivatives therein. Alternatively, together β and γ form a second bond while concurrently, δ and μ form a third bond such that the entire unit enclosed by t is a triple bond (alkyne).

[0157] In one embodiment of Formula 9:

R_1 is a 2, 3, or 4-pyridyl group.

R is a lpe, H, substituted or unsubsituted alkyl or aryl group.

a,b,d, f ,g, t and e = 1

R_2 = $-(CH_2)_8$ to $-(CH_2)_2-$

R_3 = H, lpe, substituted or unsubsituted alkyl or aryl group.

R_4 = H, lpe, substituted or unsubsituted alkyl or aryl group.

R_5 = $-(CH_2)_4-$ to $-(CH_2)-$

R_6 is a lpe, H, substituted or unsubsituted alkyl or aryl group.

R_7 = H, lpe, substituted or unsubsituted alkyl or aryl group.

E, G, J, Y, W = independently O, N, S, C=O, CH, CH_2

X = H, F, or Cl

U, L, M and Q can independently be C, CH, CX, or N.

β or γ is either CH_2, O, N, or S and together with the other, form a cis or trans cyclopropane, double bond, epoxide, aziridine, or episulfide.

When both ρ or σ and δ or μ are double bonds, a triple bond results.

R_8 = CH=CH-; C=O; or CH_2

R_9 = H, substituted or unsubstituted alkyl group, or nontoxic metal salt.

Z = $COOR_9$ or 5-substituted 1,3-thiazolidine-2,4-dione, 5-substituted-2H-tetrazole; 3-substituted-pyrrole-2,5-dione.

[0158] In one particular embodiment of Formula 9:

R_1 is a 4-N-methylpiperidinyl ring.

R is H

G is CH

b,d,f = 0; a,g, t and e = 1

R_2 = $-(CH_2)_8$ to $-(CH_2)_2-$

R_5 = $-(CH_2)_2-$ to $-(CH_2)_4-$

R_6 is a lpe, H, substituted or unsubsituted alkyl group.

Y = O or S

X = H, F, Cl.

U, L, M and Q can independently be C, CH, CX, N.

ρ or σ is either CH_2, and together with the other, form a cis or trans cyclopropane or double bond.

When both ρ or σ and δ or μ are double bonds, a triple bond results.

R_8 = trans HC=CH

R_9 = a variously substituted alkyl group.

Z = $COOR_9$ or 5-substituted 1,3-thiazolidine-2,4-dione.

[0159] In a more particular embodiment of Formula 9:

R_1 is a thioglycinate HCl salt.

R is lpe

G is S

b,d,f,e = 0; a,g, t = 1

R_2 = $-(CH_2)_7-$

R_5 = $-(CH_2)-$

X = H

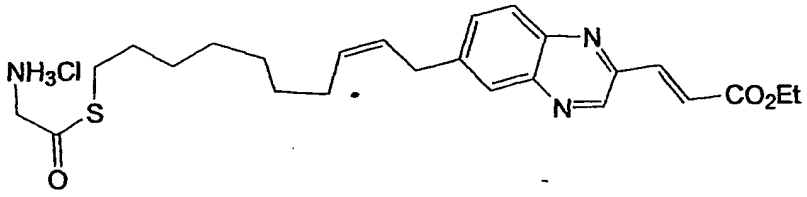
U, L = N; M, Q = CH

ρ or σ together with the other, form a cis double bond.

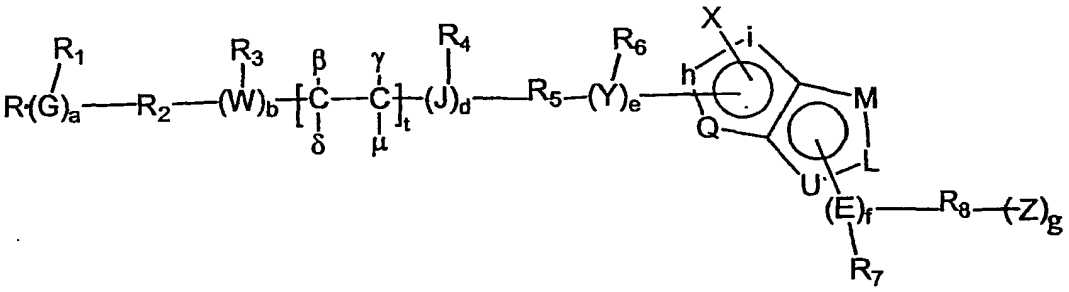
R_8 = trans -CH=CH-

Z = . CO_2Et.

In one embodiment the compound is:



[0160] Compounds are provided of Formula 10:



Where the following apply:

a = 0,1; b = 0,1; c = 0-2; d = 0,1; e = 0,1; f = 0,1, g = 0,1..

R, $R_1 - R_{11}$ = independently any combination of naught, H, lone pair of electrons, optionally substituted heteroatomic group, or alkyl, cycloalkyl, alkylcycloalkyl, arylalkyl, aryl, heteroaryl, heterocyclic, alkylheteroaryl, or alkylheterocyclic group; or optionally substituted ester, amide, carbonate, or carbamate.

W, G, E or J = independently O, N, S, $-SO_2-$,$-NHSO_2-$; $-SO_2NH-$; C, C=O, CH, or CH_2.

X = H, halogen, OR_{10}, $NR_{10}R_{11}$, SR, $-SO_2R$, $-SO_2NR_{10}R_{11}$, or $-NR_{10}SO_2R_{11}$.

Y = O, N, S, $-SO_2-$,$-NHSO_2-$; $-SO_2NH-$; C, C=O, CH, or CH_2.

U, L, Q, h, i or M can independently be CH, N, NH, S, O, or C=O.

Z = CO_2R_9; *R* or *S* or racemic 5-substituted-thiazolidine-2,4-dione; *R* or *S* or racemic 3-substituted-pyrrolidine-2,5-dione; 5-substituted-oxazolidine-2,4-dione; 5-substituted-imidazolidine-2,4-dione; 5-substituted-isoindole-1,3-dione; 3-substituted-pyrrole-2,4-dione; 3-Hydroxy-4-substituted-pyrrole-2,5-dione; 4-hydroxy-5-substituted-1,2-dihydropyrazol-3-one; 5-substituted-1,2-dihydro-pyrazol-3-one; 4-substituted-pyrazolidine-3,5-dione; 3-substituted-1H-[1,2,4]triazole; 4-substituted-2H-[1,2,3]triazole; 4-substituted-[1,2,4]triazolidine-3,5-dione; 5-substituted-2,3-dihydro-[1,2,3]triazol-4-one; 5-substituted-2H-tetrazole.

When t = 1, one of β or γ is either CH_2, O, N, or S and together with the other, form a cis or trans cyclopropane, epoxide, aziridine, or episulfide. Concurrently, δ and μ are either cis or trans to one another, and can be any combination of H, alkyl, cycloalkyl, aryl, heterocyclic, heteroaryl, alkylaryl, alkylcycloalkyl, alkylheterocyclic, alkylheteroaryl, and optionally substituted derivatives therein.

When t = 1, together β and γ form a second bond that is either cis or trans (*E* or *Z*) such that the overall unit enclosed by t is a double bond. Concurrently, δ and μ are either cis or trans to one another, and can be any combination of H, alkyl, alkoxyl, halogen, thioalkoxyl, acyloxyl, cycloalkyl, aryl, heterocyclic, heteroaryl, alkylaryl, alkylcycloalkyl, alkylheterocyclic, alkylheteroaryl, and optionally substituted derivatives therein. Alternatively, together β and γ form a second bond while

concurrently, δ and μ form a third bond such that the entire unit enclosed by t is a triple bond (alkyne).

[0161] In one embodiment of Formula 10:

R_1 is an optionally substituted heterocycloalkyl

a,b,f,c,d,g and e = 1

R_2 = $-(CH_2)_{10}$ to $-(CH_2)_4-$

R_4 = H, CH_3, ethyl, propyl

R_5 = $-(CH_2)-$ to $-(CH_2)_4-$

R_6 is a lpe, H, substituted or unsubsituted alkyl or aryl group.

J = O, N, or S

Y = O, N, or S

X = H, F, Cl, Br, or I

U, L, M, Q, h, i = independently N, NH, C, CH, S, O

β or γ is either CH_2, O, N, or S and together with the other, form a cis or trans cyclopropane, double bond, epoxide, aziridine, or episulfide.

When both ρ or σ and δ or μ are double bonds, a triple bond results.

R_8 = CH=CH- or CH_2

R_9 = H, substituted or unsubstituted alkyl group, or nontoxic metal salt.

Z = $COOR_9$; or 5-substituted 1,3-thiazolidine-2,4-dione, 3-substituted-pyrrole-2,4-dione

[0162] In one particular embodiment of Formula 10:

R_1 is a 4-piperidinyl group with an amino-acid amide bond to the ring N.

b ,f,e,d = 0; a, g = 1

R_2 = $-(CH_2)_8$ to $-(CH_2)_6-$

R_4 = CH_3

R_5 = $-(CH_2)-$ to $-(CH_2)_4-$

R_6 is a lpe, H, substituted or unsubsituted alkyl group.

A = O or S

J = O, N, or S

Y = O, N, or S

X = H, F, or Cl

U, L, M, Q, h, and i = independently CH, C, N, O, S

β or γ is either CH_2, and together with the other, form a cis or trans cyclopropane, or cis or trans double bond.

$R_8 = CH_2$

Z = 5-substituted 1,3-thiazolidine-2,4-dione, 3-substituted-pyrrole-2,4-dione

[0163] In a more particular embodiment of Formula 10:

R_1 is a 4-piperidylglycinamide HCL salt group.

R = H

G = CH

b ,f,e,d = 0; a, g = 1

R_2 = $-(CH_2)_4-$

R_5 = $-(CH_2)-$

X = H

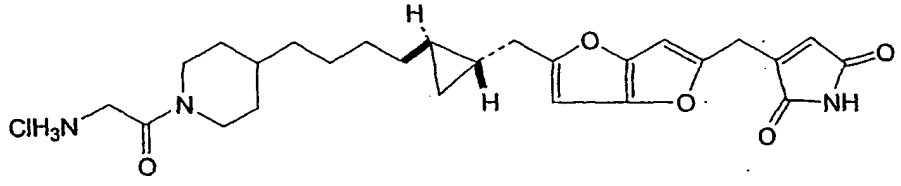
U = O; L = C; M = CH, Q = CH; h = C; i = O

β or γ is CH_2 together with the other, form a trans cyclopropane.

$R_8 = CH_2$

Z = 3-substituted-pyrrole-2,4-dione.

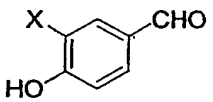
In one embodiment the compound is:



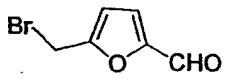
Schemes for Preparation of Compounds of the Disclosed Formulas

[00100] In view of the foregoing schemes, the disclosure herein, and knowledge in the art, the synthesis of the compounds of the invention described herein is possible by one skilled in the art of organic synthesis. Techniques available in the art are described, for example, in J. A. Joule and K. Mills "Heterocyclic Chemistry", Fourth Edition, Blackwell Science, Oxford. (2000), pp. 1-589; Gilchrist, T. L. "Heterocyclic Chemistry" 3rd Ed., Longman, Essex (England), 1997, pp. 1-414 pgs; "The Chemistry of Heterocyclic Compounds", Vols. 1-58, John Wiley & Sons, N.Y. 1950-1984 (Weissberger, A., Editor); 1985-current (E. C. Taylor, Ed.).

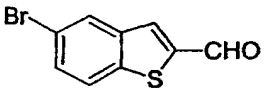
[00101] For the formulas noted, examples of starting materials that are either commercially available or have been constructed in the literature for preparing specific



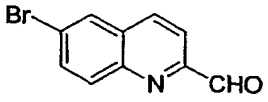
Formula 1,6; X = F, H; Commercially Available



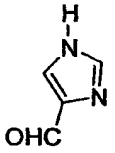
Formula 2, Commercially Available



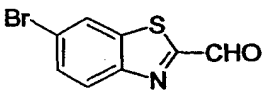
Formula 3, [7312-18-7]



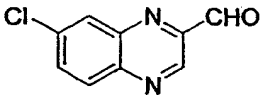
Formula 4, [59394-26-2]



Formula 7; commerically available



Formula 8, [53218-26-1]



Formula 9, [1770-42-9]

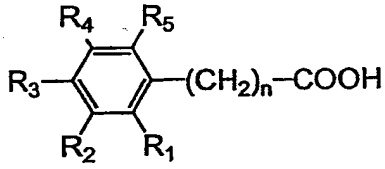
embodiments are provided by CAS registry number are shown below.

[0164] The synthetic preparation of examples for Case 1 is presented in the following Schemes. In these cases, substituted acids are required for coupling with appropriate amines to obtain required targets. Some representative acids are shown in Scheme 1,

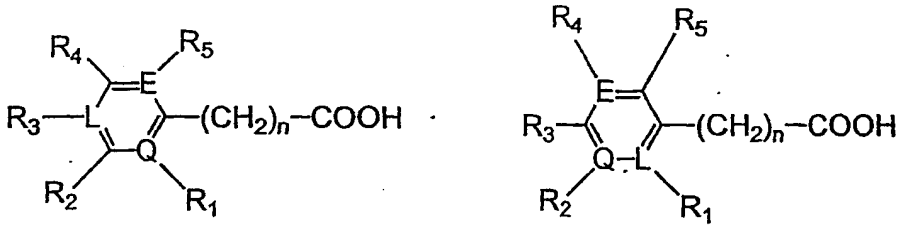
such as the cycloalkyl-alkyl acids 1-5; the aryl-alkyl acids 6-11; and the heteroaryl-alkyl acids 6h – 11h. The acids are selected from Scheme 1 but are not restricted by the Scheme. For example, a quinolinylalkyl acid is representative of a benzo fused-heteroaryl alkyl acid. On the other hand, heterocycloalkyl R groups are represented by piperidinyl or piperazinyl moieties, or any other optionally substituted heterocyclic ring system such as those containing O, N and/or S, SO SONH, SO_2NH, or SO_2. The acids 1-11 and 6h–11h are available commercially or can be prepared by known methods.

Scheme 1

1, cyclohexyl hexanoic acid, m = 4, n = 5
2, cyclopentyl hexanoic acid, m = 4, n =4
3, cyclopropyl hexanoic acid, m = 4, n =3
4, cyclohexyl pentanoic acid, m = 4, n = 4
5, cyclopentyl pentanoic acid, m = 3, n = 4



6, 5-Phenylvaleric acid, R_1=R_2=R_3=R_4=R_5=H, n = 4
7, 4-phenylbutyric acid, R_1=R_2=R_3=R_4=R_5=H, n = 3
8, 3-Phenylpropionic acid, R_1=R_2=R_3=R_4=R_5=H, n = 2
9, 5-Phenylacetic acid, R_1=R_2=R_3=R_4=R_5=H, n = 1
10, 3-(3,4-dimethoxyphenyl)propionic acid, R_1,R_4,R_5=H, R_2=R_3=OMe, n = 2
11, 3-(3,4-dimethoxyphenyl)acetic acid, R_1,R_4,R_5=H, R_2=R_3=OMe, n =1



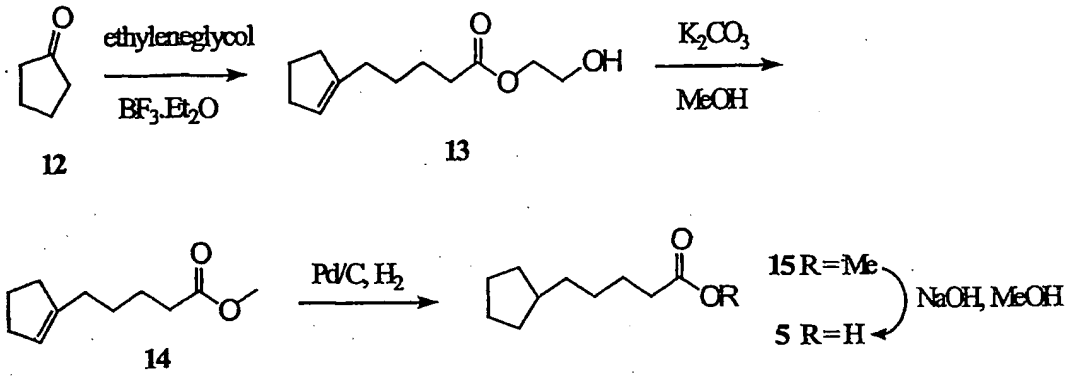
6h, 5-(2-pyridyl)valeric acid, R_1= lp; R_2=R_3=R_4=R_5=H; Q = N; L, E = C, n = 4
7h, 4-(2-pyrididinyl)butyric acid, R_1,R_5=lp; R_2=R_3=R_4=H; Q,E = N; L = C; n = 3
8h, 3-(3-pyrimidinyl)propionic acid, R_1,R_3=lp; R_2=R_4=R_5=H, Q, L=N, E= C, n = 2
9h, 2-(4-pyridyl)acetic acid, R_1=R_2=R_3=R_5=H, R_4=lp; L=N; Q, E=C; n = 1
10h, 2-(3,4-dimethoxypyridyl)propionic acid, R_1=lp; R_2=R_5=H, R_3=R_4= OMe, Q=N; E,L=C; n = 2
11h, 2-(4,5-dimethoxypyrimidinyl)acetic acid, R_1=R_5lp; R_4=H, R_3=R_4= OMe,Q,E=N; L=C; n = 1

(lp = lone pair of electrons)

[0165] As examples, the synthesis of compounds 17, 18, and 20 is shown (Scheme 3) in which, as Case 1, the following conditions apply: R = cyclopentyl; u,r,c,b,e,f,s,i and k = 0; A,Y = O (at para position); h,q,m,n,o and p = 1; R_2,R_3,R_6,R_7,R_{10},R_{11},X, = H; a = 4; J = N, R_1 = CH_3; d = 2; L,Q,U, V, □ and M = CH; and Z = $CO_2CH_2CH_3$ (17); Z = CO_2H (18); or Z = thiazolidine-2,4-dione (20).

[0166] A precursor for Scheme 3, 5-(Cyclopentyl)pentanoic acid 5, is prepared by employing a modified procedure to the one reported (Nagumao,et al. *Tetrahedron* 49 (46), 1993, 10501-10510) starting from cyclopentanone 12 as shown in Scheme 2. Self-condensation of cyclopentanone 12 in the presence of ethylene glycol and boron trifluoride-etherate furnishes the hydroxy ethyl ester 13. Transesterification with methanol and potassium carbonate converts 13 into the methyl ester 14. Catalytic hydrogenation reduces the double bond to give methyl 5-(cyclopentyl)pentanoate 15. Ester hydrolysis of 15 occurrs readily using sodium hydroxide to give the desired acid 5.

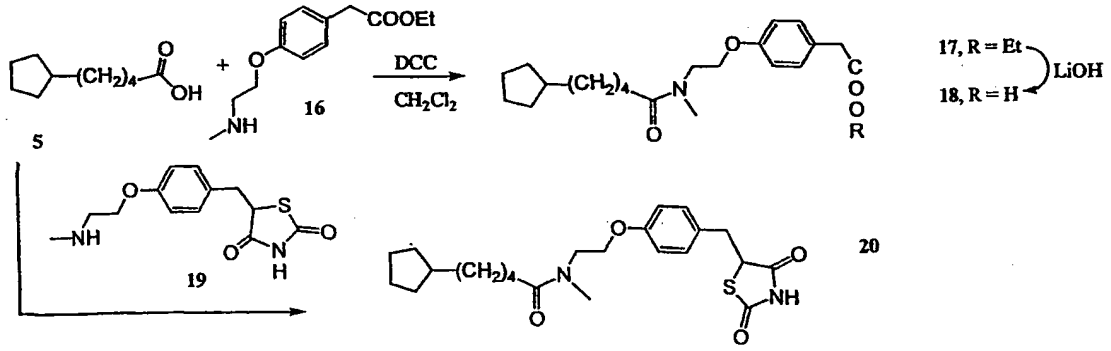
Scheme 2



[0167] With the requisite acid(s) in hand, amide formation with the appropriate amines furnishes the desired targets. Linking the amine 16 with the acid 5 occurs under activation of the carboxylic acid with dicyclohexylcarbodiimide (DCC) to give the desired target 17 as shown in Scheme 3.

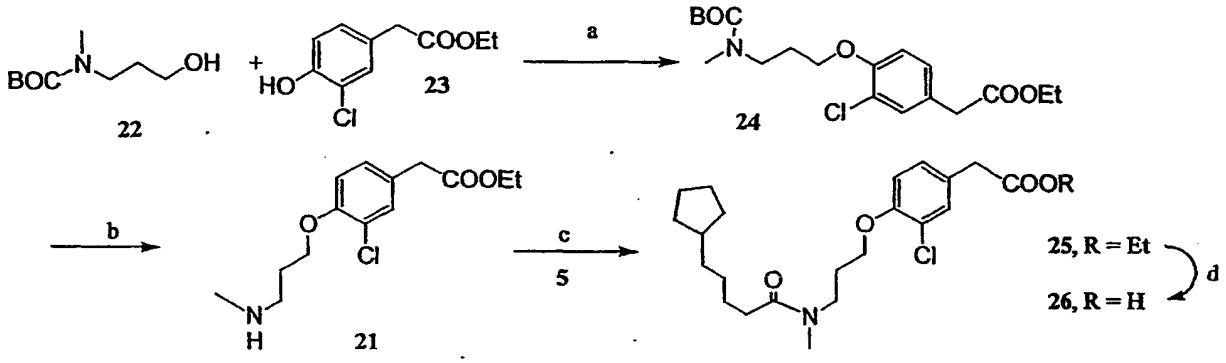
[0168] Other common methods of carboxylate activation such as by conversion to the acid chloride, N-hydroxysuccinamide/DCC, N-hydroxybenzotriazole/diisopropylcarbodiimide, etc. can be employed as well for these couplings. Hydrolysis of the ester 17, a prodrug of the bioactivated free acid, provides carboxylic acid 18. Alternatively, coupling of the known amino-thiazolidinedione 19 with acid 5 leads to the production of the cyclopentyl terminated thiazolidinedione 20.

Scheme 3



[0169] In Case 1, when R = cyclopentyl; u,r,c,b,e,f,s,i and k = 0; A,Y = O (at *para* position); h,q,m,n,o and p = 1; R_2,R_3,R_6,R_7,R_{10},R_{11}; a = 4; J = N, R_1 = CH_3; L,Q,U, V, α and M = CH; and Z = $CO_2CH_2CH_3$, d = 3 and X = *m*-Cl, the ethyl ester 25 is obtained (Scheme 4). Hydrolysis of this ester gives the carboxylic acid 26. The homologated precursor, amine (Berger, et al, *J.Biol, Chem,* 1999. 274: p. 6718-6725) 21, which is one carbon atom longer than 19, is prepared as shown in Scheme 4.

Scheme 4



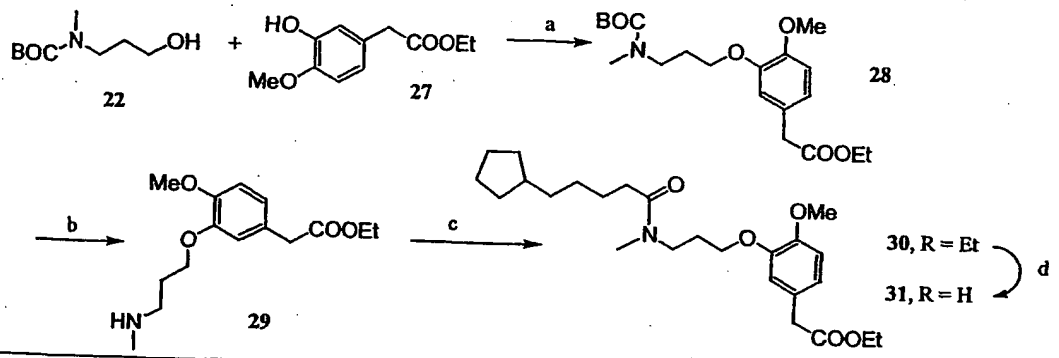
Key: a) **22**, MsCl, Pyridine and then (**23** + NaH); b) HCl, dioxane; c) DCC, dichloromethane, triethylamine and **5**; then add **21**; and d) NaOH, MeOH, water.

[0170] The phenol 23 is coupled with the *t*-BOC alcohol 22 via its mesylate to furnish the *t*-BOC protected amine 24. The *t*-BOC protecting group is removed by acid treatment to furnish the desired amine 21. As in other cases, the final acid coupling occurs readily to afford the target amide 25. Hydrolysis of 25 smoothly furnishes the acid 26.

[0171] A similar strategy may be employed to prepare targets from Case 1, where $(Y)_p$ is oriented *meta* and X = *para*-methoxy as shown in Scheme 5. The alcohol 22 is coupled with ethyl homovanillate 27 to give the *meta* oriented *t*-BOC compound 28. Deprotection of the *t*-BOC group furnishes the desired amine 29, which is coupled with acid 5 (or other examples, e.g. 1-11, 6h-11h) to give ethyl ester 30. Hydrolysis, as

before, gives the acid 31. For targets as in Case 1, where Z is thiazolidinedione, a slightly different strategy is employed as depicted in Scheme 6. Isovanillin 32 is first coupled with *t*-BOC alcohol 22 via the mesylate to furnish the aldehyde 33.

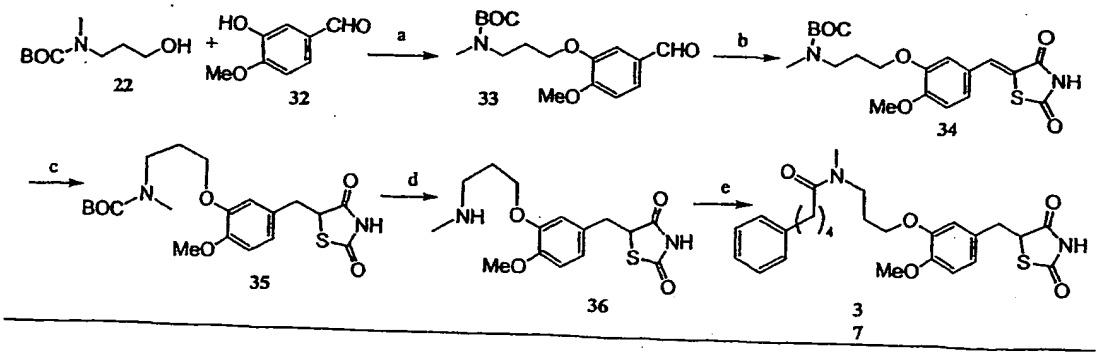
Scheme 5



Key: a) 22, MsCl, Pyridine and then (27 + NaH); b) HCl, dioxane; c) DCC, dichloromethane, triethylamine and 5; then add 21; and d) NaOH, MeOH, water.

[0172] The aldehyde 33 thus formed is then condensed with thiazolidinedione (Bernhard, et al. *J. Med. Chem.* 35, 1992, 1853-1864; Clark, et al. *J. Med. Chem.* 34, 1991, 319-325), to provide the adduct 34, which is reduced using sodium dithionite to give the desired TZD compound 35. Deprotection of the *t*-BOC group gives the amine 36, which is coupled with desired acids (e.g. 1-11, 6h-11h), which in Scheme 6 was phenylvaleric acid 6.

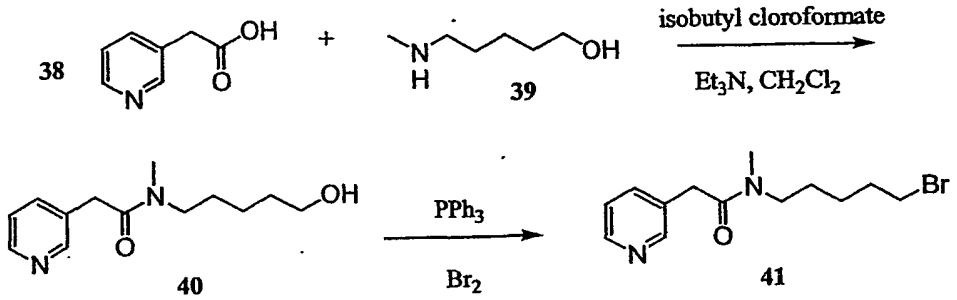
Scheme 6



Key: a) **22**, MsCl, pyridine and then (**32** + NaH); b) 2,4-Thiazolidinedione, NaOAc, AcOH; c) Sodium dithionite; d) HCl; dioxane; and e) DCC, dichloromethane, triethylamine and **6**; then add **36**.

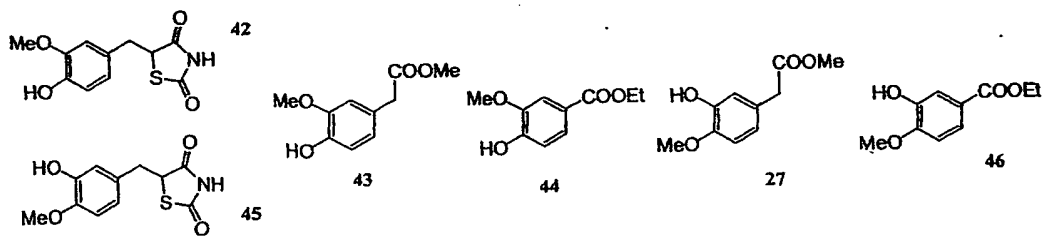
[0173] In certain instances a totally different approach needs to be employed to prepare these targets as represented in Scheme 7.

Scheme 7



[0174] The acid 38 is first coupled with the amino alcohol 39 via the mixed anhydride prepared *in situ* using isobutyl chloroformate and triethylamine. The resulting alcohol 40 is then converted to the bromide 41 using bromine and triphenylphosphine. Wagner,et al. *J. Chem. Soc. Chem. Comm.* 1989, 1619. With the bromo compound 41 in hand, coupling to the phenols 34-39 corresponding to the different structural classes via the phenoxides provides the desired targets.

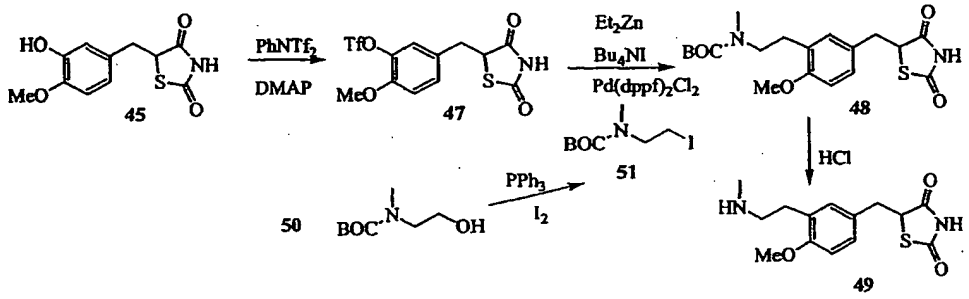
Scheme 8



[0175] For those targets as in Case 1, where p = 0 a different strategy is employed, as described in Scheme 9. The phenol 45 is converted to the triflate 47 by treating it with $PhNTf_2$ in the presence of DMAP.

[0176] The triflate 47 is then coupled with the iodocompound 51 (Piber, et al. *Org. Lett.* 1999, 1323-1326), which is prepared from its alcohol 50 by treating with iodine and triphenylphosphine, to give the *t*-BOC compound 48. The *t*-BOC group is removed in the presence of acid to give the free amine 49 which is coupled with the acids 1-11, 6h-11h to arrive at the targets as shown in Scheme 9.

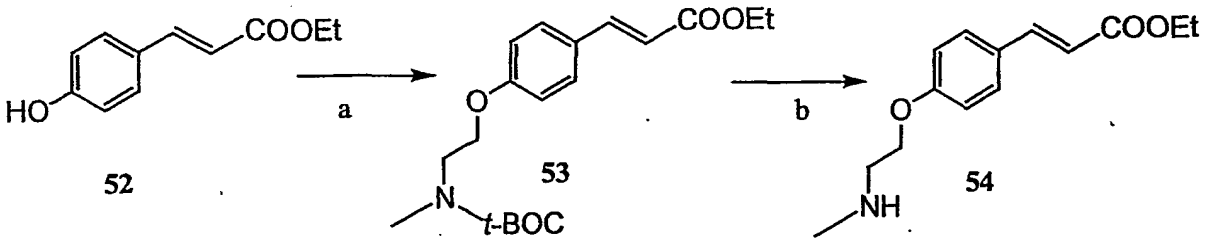
Scheme 9



[0177] Cinnamates such as 55-58 (Scheme 11) are excellent stereoelectronic mimetics for the corresponding thiazolidine-2,4-diones (e.g. 56 vs. 20). An overlay of 20 with 56 (Figure 1) shows near perfect alignment of the acidic protons, the aryl rings, and the terminal cyclopentyl rings. These same space-filling and hydrogen bonding capabilities are confirmed in docking studies with PPAR-γ.

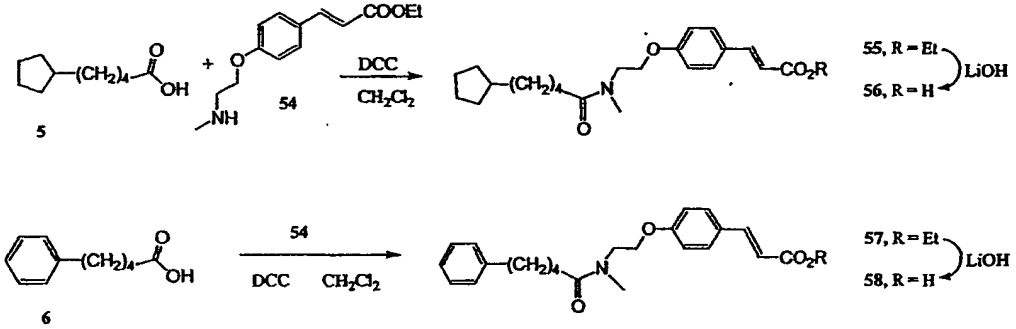
[0178] A prodrug of the carboxyl group is a logical necessity for optimization of oral or topical bioavailability, such as, but not limited to, the simple ethyl ester 55. Synthesis of 55 and 56 follow from previous schemes, and are shown in Schemes 10 and 11. The first step is to prepare the cinnamyl amine (54, Scheme 10) followed by coupling to a carboxylic acid. In Scheme 11, the cyclopentyl (55, 56) and phenyl (57, 58) R groups were arbitrarily selected as examples of the method.

Scheme 10



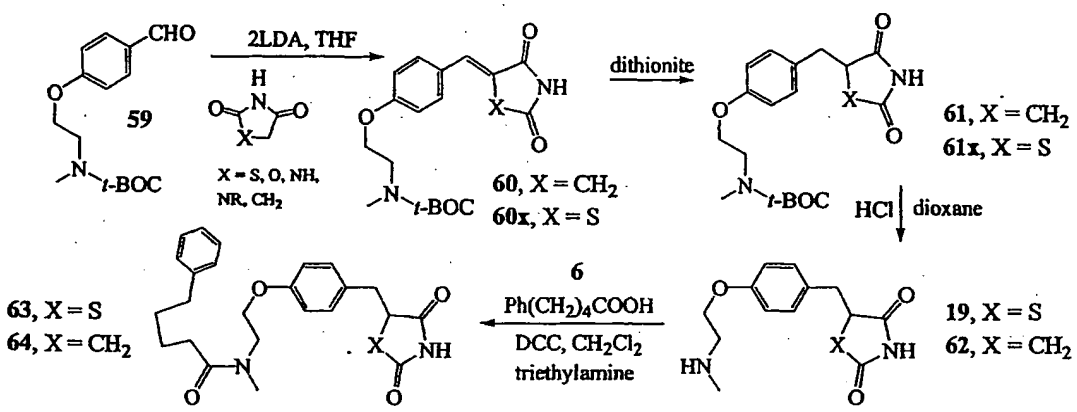
Key: a) 22, MsCl, pyridine and then (52 + NaH); b) HCl, dioxane.

Scheme 11



[0179] In addition to benzoic acids, arylacetic acids, aryloxyacetic acids, cinnamic acids, and 5-thiazolidine-2,4-diones (TZD), many other acidic moieties can substitute successfully for the TZD "head group" of PPAR-α,γ and/or δ ligands. A limited set of examples of heterocyclic "head groups" that can substitute for the TZD moiety is shown in Figure 2. For example, the succinamide analog 64, a 3-substituted pyrrolidine-2, 5-dione in which X = CH_2, could be prepared as shown in Scheme 13.

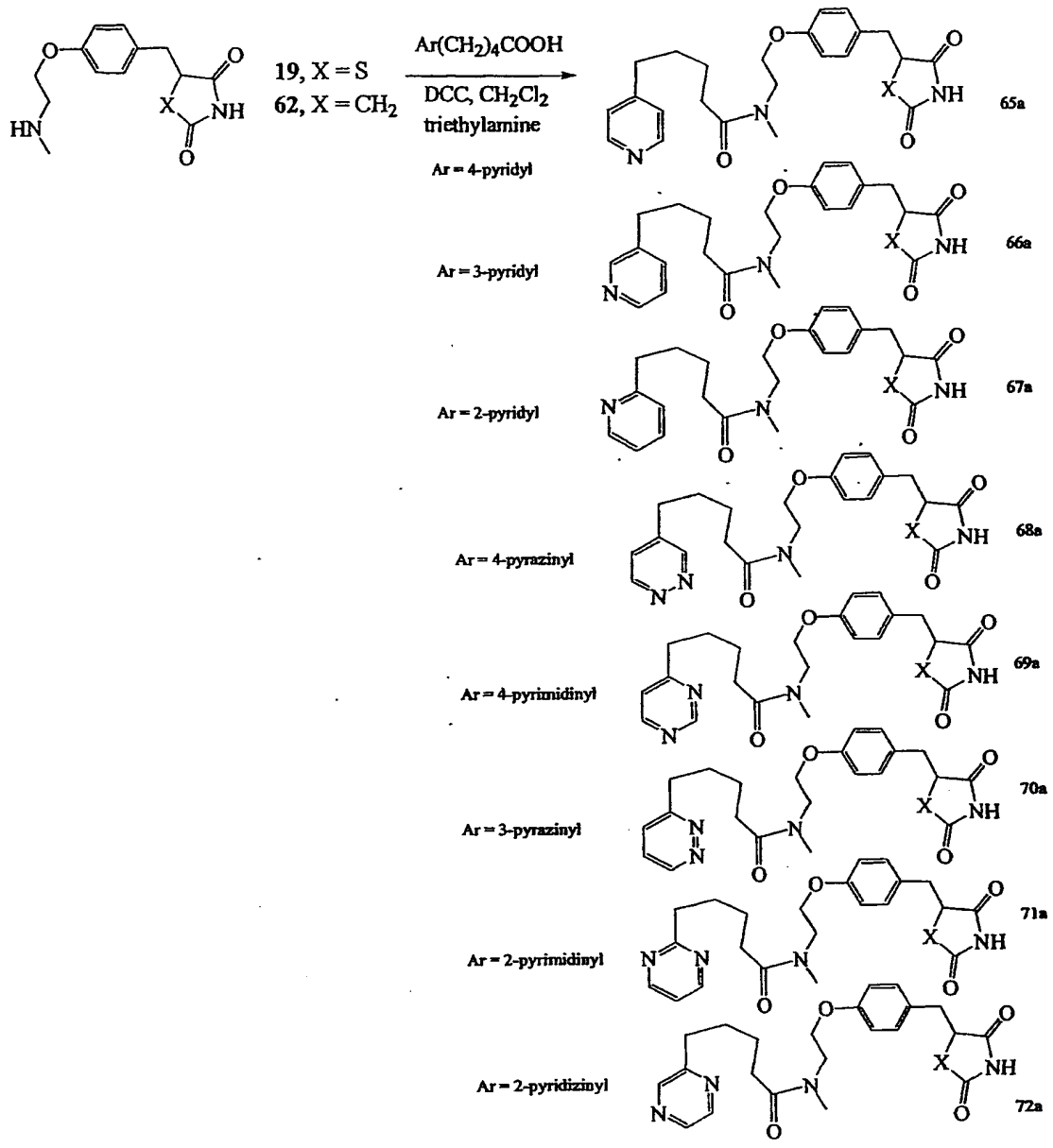
Scheme 13



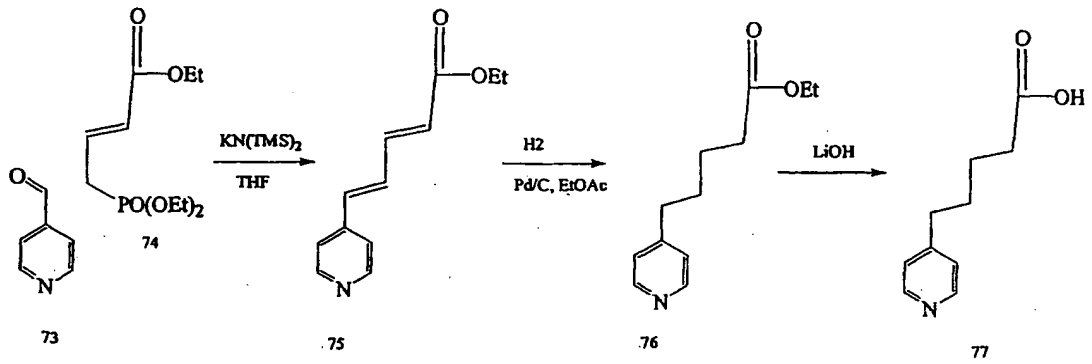
[0180] Alternatively, when X = S, the thiazolidinedione 63 is afforded. Using the known *t*-BOC protected benzyaldehyde-amine 59 for Aldol condensation with succinamide furnishes the conjugated benzylidenylsuccinamide 60, or TZD analog, 60x. Reduction, as with the TZD analog, occurs with dithionite to give either 61x (X = S), or alternatively, occurs readily with hydrogenation conditions (H_2/Pd-C), or even dissolving metal (Al-Hg amalgam, wet THF) when X = CH_2, to give 61. Now, as before, *t*-BOC deprotection with anhydrous HCl in dioxane affords 62, and finally, coupling of the amine with whatever carboxylic acid is desired, in this case 6 is selected, to provide targets 63 or 64. Obvious extensions of the chemistry presented to this point are to include heteroatoms via the azine and dizaine classes, and to prepare the corresponding carboxylic acids for coupling with 19 or 62 as before in Scheme 13.

[0181] While many other possibilities exist, the synthesis of 65 as in Scheme 14 is instructive for the entire class, essentially, and is based on the availability of the corresponding azine aldehyde. The route to interconvert the aryl aldehyde to the saturated acid is simply to conduct a crotonic phosphonate derived Horner Emmons condensation to homologate the aldehydes up to the corresponding pentadieneoic acids as shown in Scheme 15.

Scheme 14

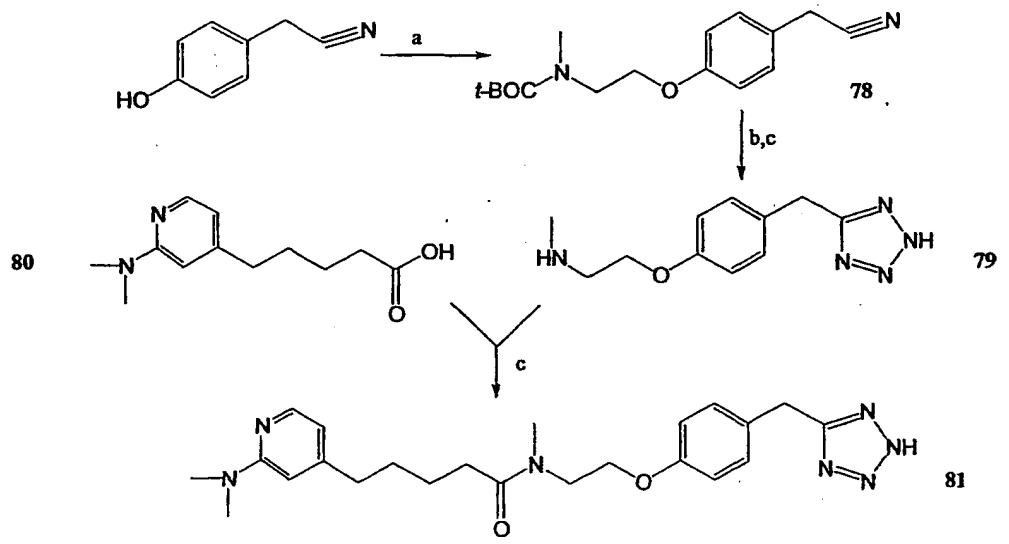

19, X = S
62, X = CH2
Ar(CH2)4COOH
DCC, CH2Cl2
triethylamine
Ar = 4-pyridyl
65a
Ar = 3-pyridyl
66a
Ar = 2-pyridyl
67a
Ar = 4-pyrazinyl
68a
Ar = 4-pyrimidinyl
69a
Ar = 3-pyrazinyl
70a
Ar = 2-pyrimidinyl
71a
Ar = 2-pyridizinyl
72a

Scheme 15



[0182] The 2*H*-tetrazole ring is a good isoelectronic replacement for a carboxylic acid or TZD group. As shown in Scheme 16, the tetrazole variant 81 is readily prepared from the corresponding nitrile 78 upon treatment with azide ion, followed by *t*-BOC deprotection and coupling to the pyridyl acid 80.

Scheme 16



Key: a) **22**, MsCl, pyridine, CH_2Cl_2; then [(*p*-hydroxyphenyl)acetonitrile + NaH]; b) NaN_3, DMF; c) HCl, dioxane; d) DCC, then **79**.

[0183] Other non-limiting examples of possible Z groups is provided by the 5-substituted 1,2-dihydropyrazol-3-one 69, the 4-substituted 1,2-dihydropyrazol-3-one 70, the 4-substituted pyrazolidine-3, 5-dione 71, or the β-lactam derivative, a potentially subversive substrate, shown in Figure 3.

METHODS OF USE OF THE COMPOUNDS

[0184] The compounds can be used in a variety of therapeutic applications.

[0185] This invention relates to the prevention and treatment of diseases involving tissues that express PPARgamma and/or PPARalpha, and/or PPARdelta and to new methods for treating inflammatory, proliferative, degenerative diseases, and diseases involving angiogenesis and neovascularization, deriving from organs and tissues of all embryological origins. These include vitreoretinopathies and uveitis, hereditary and non-hereditary degenerative neural (e.g. multiple sclerosis) and retinal diseases (e.g. retinitis pigmentosa), diseases resulting from hypoxia or vascular ischemia (e.g. ischemic heart disease), diseases involving angiogenesis and neovascularization (e.g. neoplastic diseases), age-related degenerative diseases (e.g. of the retina and skin) such as those associated with diabetes, ischemia and aging, and degenerative or dystrophic diseases or involving premature apoptosis (e.g. retinal dystrophies and retinopathies resulting from glaucoma), and chronic systemic diseases (e.g. diabetes, congestive heart failure, asthma, chronic obstructive pulmonary disease, cardiomyopathy, hypertension, atherosclerosis, myocardial fibrosis, osteoporosis, inflammatory bowel diseases). This invention relates to the treatment of diseases tissues and organs regardless of etiological agent. For example, the treatment of corneal injury or ulceration caused by unrelated etiological agents: 1) foreign body (e.g. contact lens), infectious agent (e.g. candida albicans, chlamydia trachomatis, cytomegalovirus or human immunodeficiency virus), physical agent (e.g. UV radiation), chemical agent (e.g. acids, caustic solvents) chronic systemic disease (e.g. autoimmune or collagen vascular diseases).

[0186] The invention can be used to treat various diseases. Some examples of specific embodiments of this invention are described below.

[0187] The compounds can be used to treat the group of metabolic diseases associated with insulin resistance, that consists of: obesity, type 2 diabetes mellitus, gestational diabetes, impaired glucose tolerance, Cushing's syndrome (e.g. secondary to chronic glucocorticoid therapy), polycystic ovarian syndrome. The compounds can be used to treat the metabolic disease, osteoporosis.

[0188] The compounds can be used to treat inflammatory, proliferative or degenerative skin disease, such as psoriasis, keratitis, hidradenitis, ichthyosis, acne vulgaris, rosacea, verrucae and other HPV infections, atopic dermatitis, allergic dermatitis, chemical (irritant) dermatitis, seborrheic dermatitis, solar dermatitis, acute and chronic eczema, seborrheic keratosis, senile keratosis, actinic keratosis, photo-induced keratosis, skin aging, thinning skin, dry skin, wrinkle formation, photo-induced skin aging, keloids, lichen planus, acute or chronic pruritus.

[0189] The compounds can be used to treat occlusive vascular disease, such as atherosclerosis, thrombosis, thromboembolism, restenosis after an invasive procedure (e.g. angioplasty and vascular grafting).

[0190] The compounds can be used to treat cardiovascular disease, such as arteritis, endarteritis, endocarditis, myocarditis, arterial plaque (fibrous cap) rupture, acute coronary syndrome, unstable angina, myocardial infarction, myocardial ischemia, ischemic cardiomyopathies, non-ischemic cardiomyopathies, post-myocardial infarction cardiomyopathy and myocardial fibrosis, drug-induced cardiomyopathy, congestive heart failure.

[0191] The compounds can be used to treat occlusive vascular disease associated with hyperglycemia, hyperinsulinemia, or obesity.

[0192] The compounds can be used to treat ophthalmic inflammatory disease such as uveitis, uveoretinitis, panuveitis, retinitis, iridocyclitis, immunological endophthalmitis,

choroiditis, vitreitis, keratitis, dry eye syndrome, corneal ulceration, age-related macular degeneration, glaucoma, conjunctivitis, and conjunctival ulceration, and neovascular proliferative disease such as age-related macular degeneration, exudative macular degeneration, atrophic macular degeneration, crystalline retinopathy, retinal toxicosis of systemic medications, idiopathic central serous choroidopathy, macular edema, or primary or secondary retinal detachment.

[0193] The compounds can be used to treat inflammatory disease such as retinovascular disease or retinopathy, vitreoretinopathy or vasculopathy of vasculo-occlusive or idiopathic etiology, or associated with telangiectasias or aneurysms, or associated with lupus erythematosus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, uveoretinitis or diabetes mellitus, or associated with intraocular surgery or primary or secondary retinal detachment resulting from a disease or injury.

[0194] The compounds can be used to treat inflammatory autoimmune disease mediated by T lymphocytes, such as chronic rheumatoid arthritis, juvenile rheumatoid arthritis, systemic lupus erythematosus, Hashimoto's disease, Crohn's disease, ulcerative colitis, type 1 diabetes mellitus, autoimmune neuritis.

[0195] The compounds can be used to treat inflammatory, degenerative disease such as steatosis, fibrosis, and/or cirrhosis of the liver induced by drugs (e.g. HMG-CoA inhibitos, isoniazid), chronic alcohol consumption, or resulting from poisonous toxins (e.g. mushroom poisoning).

[0196] The compounds can be used to treat inflammatory disease that is a result of rejection of an allograft transplantation and is associated with acute allograft rejection, chronic allograft rejection, graft versus host disease.

[0197] The compounds can be used to treat inflammatory disease that is a neuro-degenerative such as Alzheimer's disease, HIV-related dementia, Parkinson's disease, amyotropic lateral sclerosis, multiple sclerosis, Guillain-Barre syndrome, chronic pain,

allodynia, encephalitis, encephalomyelitis, neuritis, myesthenia gravis, Eaton-Lambert syndrome, congenital and secondary ataxias.

[0198] The compounds can be used to treat inflammatory disease that are non-carcinogenic and ischemic such as disease associated with angiogenesis and neovascularization (e.g. ischemic heart disease, retinal and choroidal angiogenesis).

[0199] The compounds can be used to treat proliferative, inflammatory disease such as angiogenesis and neovascularization that is associated with a carcinogenic (neoplastic) disease.

[0200] The compounds can be used to treat carcinogenic disease such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, enthotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelimoa, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, and retinoblastoma.

[0201] The compounds can be used to treat inflammatory disease associated with dysfunction of a T lymphocyte, or T lymphocyte subtype, leading to development of an autoimmune disease.

[0202] The compounds can be used to treat any disease that involves pathological apoptosis (programmed cell death). A compound of this invention may be effective to slow, reverse, prevent or treat said disease, wherein the disease is an ischemic disease

(cardiomyopathies, congestive heart failure), atherosclerosis, or an autoimmune disease (multiple sclerosis, Alzheimer's disease, Parkinson's disease, hepatic fibrosis or cirrhosis, myelodysplasis, arthritis and joint-disease).

[0203] The compounds can be used to treat pulmonary disease such as asthma, chronic obstructive pulmonary disease, reactive airway disease, pulmonary fibrosis, or pulmonary hypertension.

[0204] The methods of treatment in one aspect of this invention are practiced by administering to a human in need thereof a dose of a compound (or pharmaceutically acceptable salts and solvates thereof in acceptable pharmaceutical excipients) that modifies the activity of PPAR. The methods include treating a human subject prophylactically to alter inflammation, apoptosis, proliferation, angiogenesis, neovascularization, immune dysfunction, and expression of oncogenes and other genes controlling cell metabolism. The present method includes both medical therapeutic and/or prophylactic treatment, as necessary.

[0205] The methods of treatment provided by this invention are practiced by administering to a human or vertebrate animal in need a dose of a compound, or a pharmaceutically acceptable salt, ester, solvate or tautomer thereof, that activates either PPARgamma, or PPARalpha, or PPARdelta or compounds that activate more than one of these receptors. In another aspect, the novel compounds used to practice this invention are set forth above. The specific diseases and associated disorders that can be treated with the compounds described in this invention are listed in Tables I through X. Using a method of the invention, therapeutic compounds are typically administered to human patients topically to the skin or mucous membranes, by extra-ocular application, intraocularly (by chemical delivery system or invasive device), or systemically (e.g. sublingually, by suppository, by oral ingestion, intradermally, by inhalation, intramuscularly, intra-articularly, intravenously, or other parenteral route). Parenteral administration by a particular route is used in appropriate circumstances apparent to the practitioner. Oral administration is the preferred route for chronic diseases. Topical

administration is the preferred route for dermatological diseases. Extra-ocular application is the preferred route for ocular diseases involving the anterior segment of the eye, or chronic diseases Preferably, the compositions are administered in unit dosage forms suitable for single administration of precise dosage amounts.

[0206] To prepare a topical formulation for the treatment of ophthalmological or dermatological or other disorders listed in Tables I through X, a therapeutically effective concentration of the compound in one embodiment is placed in a vehicle such as a dermatological one that is known in the art. The amount of the therapeutic compound to be administered and the compound's concentration in the topical formulations depend upon the vehicle, delivery system or device selected, the clinical condition of the patient, the side effects and the stability of the compound in the formulation. Thus, the physician employs the appropriate preparation containing the appropriate concentration of the therapeutic compound and selects the amount of formulation administered, depending upon clinical experience with the patient in question or with similar patients.

ADMINISTRATION

[0207] The therapeutic compound is optionally administered topically by the use of a transdermal therapeutic system (see Barry, Dermatological Formulations, (1983) p. 181 and literature cited therein). While such topical delivery systems have been designed largely for transdermal administration of low molecular weight drugs, by definition they are capable of percutaneous delivery. They may be readily adapted to administration of the therapeutic compounds of the invention by appropriate selection of the rate-controlling microporous membrane.

[0208] For ophthalmic applications the therapeutic compound is formulated into solutions, suspensions, and ointments appropriate for use in the eye. The concentrations are usually as discussed above for topico-local preparations. For ophthalmic formulations, see Mitra (ed.), Ophthalmic Drug Delivery Systems, Marcel Dekker, Inc., New York, N.Y. (1993) and also Havener, W. H., Ophthalmic Pharmacology, C.V. Mosby Co., St. Louis (1983).

[0209] The therapeutic compound is alternatively administered by aerosol. This is accomplished by preparing an aqueous aerosol, liposomal preparation or solid particles containing the compound. A nonaqueous (e.g., fluorocarbon propellent) suspension could be used. Sonic nebulizers are preferred because they minimize exposing the therapeutic compound to shear, which can result in degradation of the compound.

[0210] Ordinarily, an aqueous aerosol is made by formulating an aqueous solution or suspension of the therapeutic compound together with conventional pharmaceutically acceptable carriers and stabilizers. The carriers and stabilizers vary with the requirements of the particular compound, but typically include nonionic surfactants (Tweens, Pluronics, or polyethylene glycol), innocuous proteins like serum albumin, sorbitan esters, oleic acid, lecithin, amino acids such as glycine, buffers, salts, sugars or sugar alcohols. Aerosols generally are prepared from isotonic solutions.

[0211] The concentration of the therapeutic compound used depends on the mode of delivery. For topical ophthalmic and extraocular formulations, the concentration of the therapeutic compound is in the range of about 0.01% weight/weight (w/w) to about 10% w/w. For example, the concentration of the therapeutic compound for this mode of delivery is in the range of about 0.025% w/w to about 2.5% w/w. Solid dispersions of the therapeutic compound as well as solubilized preparations can be used. For intraocular formulations (chemical delivery or delivery by invasive device), the therapeutic compound in one embodiment is delivered at a concentration high enough to achieve a final concentration in the range of about 0.1 micromol/L to about 10 micromol/L within the target ophthalmic compartment (e.g. the posterior chamber for the treatment of retinal diseases). Typically, for this mode of delivery, the final concentration of the therapeutic compound is in the range of about 0.25 micromol/L to about 5 micromol/L. Solid dispersions of the therapeutic compound as well as solubilized preparations can be used. Thus, the precise concentration is subject to modest but not undue experimental manipulation well within the skill of the ordinary medical practitioner in order to optimize the therapeutic response. Suitable vehicles include oil-in-water or water-in-oil

emulsions for preparation of ointments using mineral oils, petrolatum, lanolin, glycerin and the like as well as gels such as hydrogel. A preferred embodiment of the present invention involves administration of semi-solid or solid implants containing PPARgamma agonists.

[0212] Compounds useful for the application of methods described in this invention include all existing synthetic and naturally occurring PPARgamma agonists. Preferred PPARgamma agonists useful for the application of methods described in this invention include the novel compounds described in this invention and in the following submitted patent applications: Pershadsingh HA, Avery MA. 1,2-Dithiolane Derivatives, (US Patent Application No. 09/520,208) and Pershadsingh HA. Novel Dithiolane Derivatives, (US Provisional Patent No. 60/157890). Preferred PPARgamma agonists may include other drugs, which may be in slow release form for topical or systemic delivery. This may be accomplished in a preferred embodiment by using instrumentation and techniques described in U.S. Patent 5,817,075 and U.S. Patent 5,868,728.

[0213] For oral administration, either solid or fluid unit dosage forms can be prepared. For preparing solid compositions such as tablets, the compound of interest is mixed into formulations with conventional ingredients such as talc, magnesium stearate, dicalcium phosphate, magnesium aluminum silicate, calcium sulfate, starch, lactose, acacia, methylcellulose, and functionally similar materials as pharmaceutical diluents or carriers. Capsules are prepared by mixing the compound of interest with an inert pharmaceutical diluent and filling the mixture into a hard gelatin capsule of appropriate size. Soft gelatin capsules are prepared by machine encapsulation of a slurry of the compound of interest with an acceptable vegetable oil, light liquid petrolatum or other inert oil. Fluid unit dosage forms for oral administration such as syrups, elixirs and suspensions can be prepared. The water soluble forms can be dissolved in an aqueous vehicle together with sugar, aromatic flavoring agents and preservatives to form a syrup. An elixir is prepared by using a hydroalcoholic (e.g., ethanol) vehicle with suitable sweeteners such as sugar and saccharin, together with an aromatic flavoring agent.

Suspensions can be prepared with an aqueous vehicle with the aid of a suspending agent such as acacia, tragacanth, methylcellulose and the like.

[0214] Appropriate formulations for parenteral use are apparent to the practitioner of ordinary skill. In one embodiment the therapeutic compound is prepared in an aqueous solution (discussed below) in a concentration of from about 0.1 to about 100 mg/ml. More typically, the concentration is from about 1 to 10 mg/ml or about 20 mg/ml. Concentrations below 1 mg/ml may be necessary in some cases depending on the solubility and potency of the compound selected for use. The formulation, which is sterile, is suitable for various topical or parenteral routes including sublingual, by suppository (e.g. per-rectum or vaginal application), oral, intravascular, intradermal, by inhalation, intramuscular, intra-articular, intravenous, or other parenteral route.

[0215] In addition to the therapeutic compound, the compositions may include, depending on the formulation and mode of delivery desired, pharmaceutically-acceptable, non-toxic carriers or diluents, which include vehicles commonly used to form pharmaceutical compositions for animal or human administration. The diluent is selected so as not to unduly affect the biological activity of the combination. Examples of such diluents which are especially useful for injectable formulations are water, the various saline, organic or inorganic salt solutions, Ringer's solution, dextrose solution, and Hank's solution. In addition, the pharmaceutical composition or formulation may include additives such as other carriers; adjuvants; or nontoxic, nontherapeutic, nonimmunogenic stabilizers and the like.

[0216] Furthermore, excipients can be included in the formulation. Examples include cosolvents, surfactants, oils, humectants, emollients, preservatives, stabilizers and antioxidants. Any pharmacologically acceptable buffer may be used, e.g., tris or phosphate buffers. Effective amounts of diluents, additives and excipients are those amounts which are effective to obtain a pharmaceutically acceptable formulation in terms of solubility, biological activity, etc.

[0217] The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and animals, each unit containing a predetermined quantity of active material calculated to produce the desired pharmaceutical effect in association with the required pharmaceutical diluent, carrier or vehicle. The specifications for the unit dosage forms of this invention are dictated by and dependent on (a) the unique characteristics of the active material and the particular effect to be achieved and (b) the limitations inherent in the art of compounding such an active material for use in humans and animals. Examples of unit dosage forms are tablets, capsules, pills, powder packets, wafers, suppositories, granules, cachets, teaspoonfuls, tablespoonfuls, dropperfuls, ampoules, vials, aerosols with metered discharges, segregated multiples of any of the foregoing, and other forms as herein described.

[0218] Thus, a composition of the invention may include a therapeutic compound which may be formulated with conventional, pharmaceutically acceptable, vehicles for topical, oral or parenteral administration. Formulations may also include small amounts of adjuvants such as buffers and preservatives to maintain isotonicity, physiological and pH stability. Means of preparation, formulation and administration are known to those of skill. See generally Remington's Pharmaceutical Science 15th ed., Mack Publishing Co., Easton, Pa. (1980).

Slow Release Delivery

[0219] Slow or extended-release delivery systems, including any of a number of biopolymers (biological-based systems), systems employing liposomes, colloids, resins, and other polymeric delivery systems or compartmentalized reservoirs, can be utilized with the compositions described herein to provide a continuous or long term source of therapeutic compound. Such slow release systems are applicable to formulations for delivery via topical, intraocular, oral, and parenteral routes.

Delivery by Invasive Device

[0220] As mentioned above, delivery intravascularly, intra-articularly, intramuscularly, intra-articularly, intradermally, or other parenteral route can be accomplished by injection, cannula or other invasive device designed to introduce precisely metered amounts of a desired formulation to a particular compartment or tissue. For example, delivery to certain areas within the eye, in situ, can be accomplished by injection, cannula or other invasive device designed to introduce precisely metered amounts directly or contained in a reservoir for slow release in situ, of a desired formulation to a particular compartment or tissue within the eye (e.g. anterior or posterior chamber, uvea or retina). Preferably, a solid or semisolid implant can be delivered subretinally using the instrumentation and methods described in U.S. Patent 5,817,075 and U.S. Patent 5,868,728.

Routes of Administration

[0221] Therapeutic agents of the invention are usually delivered or administered topically for treating disorders involving the eye that are listed in Tables I through X. Oral administration is preferred for disorders in Tables I through X that cannot be treated effectively by topical therapy. Additionally, the agents can be delivered parenterally, especially for treatment of retinitis and degenerative retinal diseases, and for other conditions in Tables I through X, that do not respond to oral or topical therapy, or for conditions where oral or topical therapy is not feasible. Parenteral therapy is typically oral, intraocular, transcutaneous, intradermal, intrathecal, intramuscular, intra-articular, by inhalation, intravascular, sublingual, by suppository (e.g. per-rectum or vaginal application), by inhalation, or other parenteral route.

[0222] A preferred way to practice the invention for dermatological or ophthalmic disorders in Tables I through X to which this method is applicable, is to apply the compound of interest, in a cream, lotion, ointment, or oil based carrier, or some other suitable vehicle directly to the lesion. For example, the concentration of therapeutic

compound in a cream, lotion, or oil is 0.025 to 2.5%. In general, the preferred route of administration is oral, topical, intraocular or parenteral. Topical administration is preferred in treatment of lesions of the skin as in psoriasis, external eye as in conjunctivitis, keratitis, scleritis, squamous cell carcinoma, corneal erosion, dry eye syndrome, and anterior compartment of the eye as in glaucoma, uveitis and other diseases of the uveal tract, where such direct application is practical and clinically indicated.

[0223] Oral administration is a preferred alternative for treatment of other lesions discussed in Tables I through X, where direct topical application is not useful as in the treatment of chronic or acute systemic diseases, and diseases of the posterior segment of the eye, as in uveitis, glaucoma, optic neuritis or retinitis. Intravascular (intravenous being the preferred route) administration may be necessary in disorders that cannot be effectively treated by topical or oral administration. Administration by inhalation is preferred for lung diseases such as broncho-constrictive disease, asthma, and chronic obstructive pulmonary disease.

[0224] Intraocular, transcutaneous, intradermal, intrathecal, intramuscular, intra-articular injections or other invasive technique are preferred alternative in cases where the practitioner wishes to treat one or a few specific areas or lesions depending on their location within the eye. Usually, the compound is delivered in an aqueous solution. Additionally, the therapeutic compounds are injected directly into lesions (intra-lesion administration) in appropriate cases. Intradermal administration is an alternative for extraocular lesions. Intra-lesional and intradermal injections are alternative routes of application for certain lesions, e.g. extraocular neoplastic or hyperplastic lesions such as squamous cell carcinoma and condyloma, respectively. Inhalation therapy is preferred for pulmonary diseases, sublingual and intra-rectal suppository is preferred for rapid delivery or in clinical situations where delivery via the oral or intravascular route is inconvenient or problematic. Application via vaginal topical formulation or via suppository formulation is preferred for diseases localized to the vagina or other segment of the urogenital tract.

[0225] The compounds of this invention can be formulated to have a wide spectrum of solubility properties, where the oil/water diffusion coefficient (o/w) values may range from < 1 (very hydrophilic) to > 6 (very hydrophobic). For pulmonary applications, preferred therapeutic compounds are ester derivatives, formulated into solutions, suspensions, aerosols and particulate dispersions appropriate for application to the pulmonary system. The therapeutic agent may be inhaled via nebulizer, inhalation capsules, inhalation aerosol, nasal solution, intra-tracheal as a solution via syringe, or endotracheally tube as an aerosol or via as a nebulizer solution. Similarly, structures derivitized as acetates, succinates, glycinates, etc., and rendered water soluble, are best suited for delivery across the gastrointestinal mucosa.

Dosage and Schedules

[0226] An effective quantity of the compound of interest is employed in treatment. The dosage of compounds used in accordance with the invention varies depending on the compound and the condition being treated. For example, the age, weight, and clinical condition of the recipient patient; and the experience and judgment of the clinician or practitioner administering the therapy are among the factors affecting the selected dosage. Other factors include: the route of administration, the patient, the patient's medical history, the severity of the disease process, and the potency of the particular compound. The dose should be sufficient to ameliorate symptoms or signs of the disease treated without producing unacceptable toxicity to the patient. In general, an effective amount of the compound is that which provides either subjective relief of symptoms or an objectively identifiable improvement as noted by the clinician or other qualified observer. A typical dose may range from 1 mg/day to 500 mg/day of the compound depending on the ability of the compound to influence the PPAR receptors of interest and the disease under consideration.

[0227] PPARgamma/PPARalpha co-ligands (co-activators):

[0228] In one embodiment, ligands that are dual activators (co-activators) of PPARgamma and PPARalpha, are those compounds with an EC50 for PPARgamma transactivation within about 100-fold of the EC50 for PPARalpha transactivation. More typically, the preferred EC50s for PPARgamma and PPARalpha transactivation are within about 10 to 20-fold of one another. However, the EC50s for activation of PPARalpha and PPARgamma could be within 1000 fold of each other.

[0229] The EC_{50} is the concentration of a compound required to bind to or activate 50% of the receptor in a sample or a subject. Broadly, for a PPAR ligand, e.g. a thiazolidinedione, the oral dose in one embodiment may be determined from the following formula:

oral dose (in mg) = $(k_1)(EC_{50})(k_2)$ (LBW)(MW);

wherein k_1 is a dimensionless constant of 5 to 100; EC_{50} is the concentration (amount) of compound required to activate or bind to 50% of PPARgamma or PPARalpha in the sample or patient and is in mole/L units; k_2 is the fractional water content of the lean body weight (LBW) of the patient = 0.72 L/kg, (*see,* GEIGY SCIENTIFIC TABLES, VOL. 1, Lentner (ed.), p217, Giba-Geigy Ltd., Basle, Switzerland (1981); and MW is the molecular weight of the compound in g/mole.

[0230] For example, troglitazone is a compound encompassed by the methods of this invention. A man with diagnosis of early stage prostate cancer *in situ* has a lean body weight (LBW) of 70 kg. If $k_1 = 10$; the EC_{50} for troglitazone = 2.4×10^{-6} mol/L and the molecular weight of troglitazone = 442 g/mol, then the oral dose in milligrams = (10)(2.4 x 10^{-6} mol/L)(0.72 L/kg x 70 kg) (442 g/mol) or 535 mg. Similarly, an effective dose of rosiglitazone in milligrams for an average man is (10) (0.06 x 10^{-6} mol/L) (0.72L/kg x 70kg) (304 g/mole) or 9.2 mg.

[0231] Typically, the dosage per day of the a PPAR ligand of this invention will depend on the its affinity for PPARgamma or PPARalpha or PPARdelta. The dosages of compounds with high affinity, *e.g.*, like rosiglitazone, will fall between about 0.1 mg to about 10 mg per day. The dosages of compounds of intermediate affinity, e.g. like

pioglitazone, will range from about 10 mg to about 100 mg per day. The dosages of compounds with low affinity, *e.g.*, like troglitazone, will fall from about 100 mg to about 1000 mg per day.

[0232] An oral dosing schedule is typically, a single dose once a day. However, more than one dose can be given per day. Because of the lower incidence of undesirable side effects, the compounds of this invention can be given until improvement in the inflammatory process or disease involving neovascularization is observed. Because the compounds of this invention are to some degree fat-soluble, in a preferred embodiment, the compounds are administered with food. The fats in food provide a lipid micellular phase in which the particular PPAR ligand of this invention can solubilize and be more effectively absorbed.

[0233] Depending on the EC50 for PPAR activation, a dosage range for local treatment is about 0.025% to about 10% (weight/volume) in a suitable solvent applied that permits release of the compound into the prostate tissue. For high affinity ligands, a preferred range is about 0.025% to 0.1%. For intermediate affinity ligands, a preferred range is about 0.1% to 0.5%. For low affinity ligands, a preferred range is about 0.5% to 5%. One of skill will realize that the dosage for local treatment will vary depending on the compound used, its hydrophobicity and hydrophilicity, and the EC50 for PPARgamma and/or PPARalpha activation and/or PPARdelta activation. For example, the PPAR ligands of this invention may have vastly different affinities for PPARalpha and PPARgamma, or the may be similar, i.e. within about one to two orders of magnitude. Typically, the greater the affinity, the more effective the compound, and the lower the dosage that is an effective amount. Therefore, a lower concentration of a drug (with a higher affinity) in a unit dosage form comprises an effective amount.

[0234] Typically, the local dosage is administered at least once a day until a therapeutic result is achieved. The dosage can be administered twice a day, but more or less frequent dosing can be recommended by the clinician. Once a therapeutic result is

achieved, the compound can be tapered or discontinued. Occasionally, side effects warrant discontinuation of therapy.

[0235] An effective quantity of the compound of interest is employed in treatment. The dosage of compounds used in accordance with the invention varies depending on the compound and the condition being treated. The age, lean body weight, total weight, body surface area, and clinical condition of the recipient patient; and the experience and judgment of the clinician or practitioner administering the therapy are among the factors affecting the selected dosage. Other factors include the route of administration the patient, the patient's medical history, the severity of the disease process, and the potency of the particular compound. The dose should be sufficient to ameliorate symptoms or signs of the disease treated without producing unacceptable toxicity to the patient.

[0236] Broadly, an oral dosing schedule is from about 0.1 mg to about 1000 mg once or twice a day depending on the binding affinity of the compound for PPARgamma or PPARalpha or PPARdelta. For example, the typical oral dose of the thiazolidinediones, rosiglitazone and pioglitazone, presently approved for the treatment of type 2 diabetes mellitus, is 4 to 8 mg and 15 mg to 45 mg daily, respectively.

[0237] Using rosiglitazone as the prototype agent for the purpose of this invention, a convenient oral dose for an adult patient is 4 to 8 mg once a day, or 2 to 4 mg twice a day. A dosage range for topical treatment is about 0.1% to about 1% (weight/volume) in a gel, cream or ointment, applied twice a day. A usual dose for intramuscular or intraocular injection is 0.25 to 2.5 mg, depending on the compartment of the eye to be treated and on the lean body mass of the patient. A typical dosage for intra-dermal administration is about 2.5 to 25 mg per injection per site. A typical dosage for intravenous or intramuscular administration in an adult patient would be between 50 and 250 mg per day given in single or divided doses depending on the judgement of the practitioner.

[0238] Typically, the dosage is administered at least once a day until a therapeutic result is achieved. Preferably, the dosage is administered twice a day, but more or less

frequent dosing can be recommended by the clinician. Once a therapeutic result is achieved, the drug can be tapered or discontinued. Occasionally, side effects warrant discontinuation of therapy. In general, an effective amount of the compound is that which provides either subjective relief of symptoms or an objectively identifiable improvement as noted by the clinician or other qualified observer.

[0239] This invention further relates to the use of each of the subject compounds in the treatment of the diseases listed in Tables I through Table X, administered as either as a single agent, or in combination with a natural or synthetic compound selected from one or more of the following categories: PPARalpha agonist, a PPARdelta agonist, or PPARgamma agonist; a rexinoid or other RXR agonist; a vitamin D derivative or other VDR agonist; a glucocorticoid or other GR agonist; a LXR or LXR/RXR agonist (e.g. an oxysterol); a FXR or FXR/RXR agonist (e.g. farnesol, chenodeoxycholic acid, a bile acid); an HMG-CoA reductase inhibitor; a CETP inhibitor, e.g. a substituted-1,2,3,4-tetrahydroquinoline; a pharmacological agent that increases the expression or upregulates ABC1; a beta3-adrenoceptor agonist; a calcineurin inhibitor (e.g. cyclosporine A, tacrolimus, sirolimus); an anti-hypertensive angiotensin converting enzyme (ACE) inhibitor; and an anti-hypertensive angiotensin receptor blocker (ARB)

[0240] Synergistic therapeutic effects can be achieved by oral or topical administration of the drugs encompassed in the current invention together with a second agent selected from the above-identified categories of compounds, administered orally, topically or intravenously. A preferred dosage range for administration of a retinoic acid derivative or retinoid would typically be from 0.1 to 100 mg per square-meter of body surface area, depending on the drug's ability to bind to or modify the activity of its cognate nuclear receptor, given in single or divided doses, orally or by continuous infusion, two or three times per day. For synergistic therapy, the preferred dosages and routes and frequency of administration of the vitamin D analogs or retinoid compounds can be similar to the dosages and routes and frequency of administration ordinarily recommended for these agents when given without PPARgamma activators. Examples of

effective retinoids are 9-cis-retinoic acid, 13-cis-retinoic acid, all-trans-retinoic acid (at-RA). Preferred retinoids for this purpose would include 13-cis-retinoic acid, tazarotene, or Targretin. A preferred dosage range for systemic administration of a vitamin D analog would typically be from 0.1 to 100 mg per square-meter of body surface area, depending on the drug's ability to bind to and or activate its cognate vitamin D receptor, given in single or divided doses, orally or by continuous infusion, two or three times per day. Examples of effective vitamin D analogs are 1,25-dihydroxy-vitamin D, calcipotriene and calcipotriol. The dosage range and routes and frequency of administration of PPARgamma activators required to achieve synergistic effects when given with vitamin D or retinoid derivatives are the same as those described elsewhere in this disclosure. The preferred mode of administration of these drugs for synergistic therapeutic purposes would be orally although alternatively one can use topical or parenteral routes of administration. The dosages and the modes and frequency of administration of the vitamin D or retinoid related compounds for synergistic topical therapy would be similar to those ordinarily recommended for these agents when given without PPARgamma activators. The dosage range and the modes and frequency required for topical administration of the flavonoid thiazolidine derivatives given in combination with vitamin D or retinoid related compounds are the same as those described elsewhere in this disclosure.

[0241] Synergistic therapeutic effects can be achieved by oral or topical administration of the drugs encompassed in the current invention together with orally, topically or intravenously administered natural or synthetic antioxidants. These include ascorbic acid and its derivatives (e.g. vitamin C), the tocopherols (e.g. vitamin E, vitamin E succinate), carotenes and carotenoids (e.g. beta-carotene), alpha-lipoic acid, probucols, flavones, isoflavones and flavonols (e.g. quercetin, genistein, catechin, apigenin, lutein, luteolin), glutathione and its derivatives (e.g. N-acetylcysteine and dithiothreitol), and phytoestrogens and phenolic anthocyanidin and procyanidin derivatives (e.g. resveratrol, cyanidin, cinnamic acid).

[0242] The compounds of the instant invention are further useful to suppress the mediators of neurogenic inflammation (e.g. substance P or the tachykinins), and may be used in the treatment of rheumatoid arthritis; psoriasis; topical inflammation such as is associated with sunburn, eczema, or other sources of itching; and allergies, including asthma. The compounds can also function as neuromodulators in the central nervous system, with useful applications in the treatment of Alzheimer's disease and other forms of dementia, pain (as a spinal analgesic), and headaches. Furthermore, in disorders involving myocardial fibrosis, myocardial ischemia, pathological conditions secondary to the autoimmune response to allograft transplantation, the splanchnic blood flow, including hepatic fibrosis, cirrhosis and oesophagal varices, the compounds of the invention can provide cytoprotection.

Screening Assays and Cell Systems

[0243] Assays for screening for compounds that modify the activity of PPARgamma and/or PPARalpha and/or PPARdelta can be conducted using methods known in the art such as PPAR transactivation (Willson *et al. J. Med. Chem.* 43:527-50 (2000)) and the fluorescence resonance energy (FRET) assay (Zhou G., *et al., Mol Endocrinol* 12(10):1594-604 (1998). In one embodiment the following cell systems are employed. Human endothelial cells and vascular smooth muscle (VSM) cells which are known to express both PPARgamma and PPARalpha can be used. Alternatively, isolated human peripheral T lymphocytes from normal healthy donors or a mammalian cell line such as a Jurkat T cell line poorly express PPARalpha and PPARgamma can be used. To test specific PPARgamma activating compounds, lymphocytes or Jurkat cells are transfected with the PPARgamma expression vector. To test mixed PPARalpha and PPARgamma activating compounds, (PPARalpha/PPARgamma co-ligands), lymphocytes or Jurkat cells are transfected with both PPARalpha and PPARgamma expression vectors. Other cells expressing PPARdelta may also be employed.

[0244] The binding of agonist ligands to the receptor results in changes in the expression level of mRNAs encoded by PPAR target genes. This process,

"transactivation", is determined by cell-based assays which monitor this functional activity. Transactivation assays use cells that have been transfected with a vector expressing the receptor as well as a second vector containing a DNA direct repeat (DR-1) response element and a reporter gene, which encodes an enzyme such as chloramphenicol acetyltransferase, secreted placental alkaline phosphatase, or firefly luciferase. Activation of the receptor by agonist ligands leads to induction of reporter enzyme expression, which can be conveniently assayed using standard colorimetric or photometric methods. A procedure used to test the compounds of this invention is the PPAR-GAL4 transactivation assay, which uses chimeric receptors where the PPAR LBD is fused to the DBD of the yeast transcription factor GAL4 and employs a reporter gene containing a GAL4 response element, and has previously been described in detail (Lehmann et al., *J. Biol. Chem.* 1995, 270, 12953-12956). Briefly, cells are incubated with 10% delipidated fetal calf serum and the test compound at the appropriate concentration. After an additional 24 h, cell extracts are prepared and assayed for alkaline phosphatase and beta-galactosidase activity. Alkaline phosphatase activity was corrected for transfection efficiency using the beta-galactosidase activity as an internal standard. Compounds which elicited on average at least 70% activation of PPAR versus rosiglitazone (positive control for PPARgamma specific activation) or versus Wy-14643 (positive control for PPARalpha specific activation) were considered full agonists (Willson et al., *J. Med. Chem.* 2000; 43:527-50; Henke et al. *J. Med. Chem.* 1998; 41:5020-36).

[0245] The scenarios described below employ representative compounds of these classes for screening assays and in examples wherein they are administered to human subjects in the treatment of specified diseases. The following examples on screening the compounds for certain functional acitivities of interest and for using the compounds to treat various clinical disorders are included for illustrative purposes and are not intended to limit the scope of methods for screening and using the compounds of the current invention.

[0246] The invention will be further understood by the following non-limiting examples.

EXAMPLES

Example 1: Method for evaluating the activity of compounds developed using this invention - Binding Assay

[0247] For the binding assay, bacterial expression plasmids for the ligand binding domains of the PPAR subtypes, cDNAs encoding the hinge and ligand binding domains of hPPAR (amino acids 167-468), mPPAR (amino acids 167-468), xPPAR (amino acids 174-474), and xPPAR (amino acids 178-477) are obtained. GST-PPAR fusion proteins or glutathione S-transferase (GST) alone as a control are expressed in BL21(DE3) plysS cells and extracts prepared by freeze-thawing the cells in bacterial lysis buffer (10 mM Tris, pH 8.0/250 mM KCl/1 mM DTT/1% Triton X-100) followed by centrifugation at 40,000 × g for 30 min. Glycerol is added to the bacterial extracts to a final concentration of 10%. Bacterial extracts are dialyzed extensively against bacterial lysis buffer containing 10% glycerol to remove glutathione that might interfere with the stability of the various FAs and eicosanoids in the competition binding assays. For saturation binding analysis or competition binding assays, bacterial extracts (50 microg protein) containing either GST-xPPAR or GST-xPPAR are incubated at 4°C for 2-3 hr in buffer containing 10 mM Tris (pH 8.0), 50 mM KCl, and 10 mM DTT with [3H]GW2331 in the presence or absence of unlabeled GW2331 or the various FAs or eicosanoids. Bound radioactivity was separated from free radioactivity by elution through 1 ml Sephadex G-25 protein desalting columns (Boehringer Mannheim). Bound radioactivity eluted in the column void volume and was quantitated by liquid scintillation counting.

[0248] Several radioligands are now available for use in conventional competition binding assays: [3H]GW 2331 for PPARalpha; [3H]rosiglitazone (BRL49653), [3H]AD-5075, and [125I]SB-23663643 for PPARgamma; and [3H]GW 243344 and [3H]L-78348345 for PPARdelta. Each of these radioligands is reported to show specific binding to the corresponding PPAR subtype. Initial PPAR binding assays used gel filtration to separate the bound radioligand from the free ligand. The use of scintillation proximity

assay (SPA) technology has greatly increased the throughput of PPAR competition binding assays. SPA beads emit light when held in close proximity to a suitable radionuclide (e.g. 3H or 125I). If the receptor is attached to the SPA bead, binding of a radioligand to the PPAR LBD leads to a readily detectable signal. Displacement of the radioligand by a test compound leaves the free radioligand in solution, where it can no longer promote emission by the SPA bead. This technology removes the need to separate free radioligand from the bound ligand, greatly simplifying automated high-throughput screening. The homogeneous format of the SPA binding assay allows determination of equilibrium binding affinities and also permits the use of relatively low-affinity radioligands.

Example 2: Method for evaluating PPAR activity of the compounds of this invention using a transactivation assay or FRET assay

[0249] The binding of agonist ligands to a nuclear receptor results in transactivation, i.e., changes in the expression level of mRNAs encoded by PPAR target genes. Cell-based assays have been developed which monitor this functional activity. Transactivation assays use cells that have been transfected with a vector expressing the receptor as well as a second vector containing a DR-1 response element and a reporter gene, which encodes an enzyme such as chloramphenicol acetyltransferase, secreted placental alkaline phosphatase (SPAP), or firefly luciferase. Activation of the receptor by agonist ligands leads to induction of reporter enzyme expression, which can be conveniently assayed using standard colorimetric or photometric plate readers.

[0250] In the case of PPARs, an ideal assay is the PPAR-GAL4 transactivation assay useing chimeric receptors where the PPAR LBD is fused to the DBD of the yeast transcription factor GAL4. This assay employs a reporter gene containing a GAL4 response element. Since mammalian cells do not contain GAL4, only the transfected PPAR-GAL4 chimeric receptors can activate the reporter gene, effectively eliminating interference from endogenous nuclear receptors. In general, PPAR agonists show

comparable potency and efficacy in assays using either the PPAR-GAL4 chimeras or the full-length receptors.

[0251] COS-1 cells are maintained as described above for the mammalian two-hybrid system. The following plasmids are used for transfection: respective reporter plasmid (1 microg) containing the pGL-GAL4-UAS (17-mer × 2--globin promoter-luciferase) cotransfected with 0.1 microg of pM(GAL4-DBD)-PPAR (DEF) or pM-PPAR (DEF-AF-2) with or without 1 microg of SRC-1, TIF2, or TRAP220 expression vector. As a reference plasmid for normalization, 10 ng of pRL-CMV plasmid (Promega) is used. Bluescribe M13+ (Stratagene) is used as the carrier to adjust the total amount of DNA to 3 microg. added to the medium 12 h after transfection and every 8 h thereafter at each exchange of medium. After 48 h, firefly luciferase activity (from GAL4-UAS) is used to measure transfection efficiency by Renilla luciferase activity (from pRL-CMV) as described previously.

[0252] Using methods know to those skilled in the art, fluorescence resonance energy tranfer (FRET) assays were used to determine the PPAR activities of representative compounds of the current invention. The assay is an approach for characterizing nuclear receptor agonists or antagonists; individual ligands and determining their potencies that are predictive of in vivo effects (Zhou, et al., Mol. Endocrinol. 12(10):1594-604 (1998)). Example 16 shows FRET assay results demonstrating PPAR activity of representative compounds of the current invention.

Example 3: Method for Screening for Compounds that Modify the Activity of PPARgamma and PPARalpha based on Inhibition of NF-kappaB activation

[0253] Compounds are tested for the ability to inhibit activity of NF-kappaB. Human endothelial cells and vascular smooth muscle cells (VSMC) are known to express both PPARgamma and PPARalpha (Neve BP, et al. Biochem Pharmacol. 2000; 60:1245-1250). Alternatively, isolated human peripheral T lymphocytes from normal healthy donors or a mammalian cell line such as a Jurkat T cell line transfected with the

PPARalpha and/or the PPARgamma expression vector may be used in these experiments. One of these selected cell types is stimulated with a concentration of one or a combination of: phytohemagglutinin/phorbol-12-myristate-13-acetate (PHA/PMA), TNF-alpha, interferon-gamma or some other factor that activates NF-kappaB. Activation of NF-kappaB is determined by electrophoretic mobility shift assay similar to that previously described (Rossi A, et al. Proc Natl Acad Sci USA 1997; 94:746-50). Preincubation of the same cells with 5 micromolar of the test compound 2 hours prior to addition of an activator of NF-kappaB inhibits the activation of NF-kappaB otherwise observed in the absence of the benzodithiolanyl derivative.

Example 4: Method for Screening for Compounds that Modify the Activity of PPARgamma and PPARalpha based on Inhibition of NFAT activation

[0254] Isolated human peripheral T lymphocytes from normal healthy donors or a mammalian cell line such as a Jurkat T cell line transfected with the PPARalpha and/or the PPARgamma expression vector, is stimulated with a concentration of one or a combination of PHA/PMA, TNF-alpha, interferon-gamma or some other factor that activates NFAT. Transcriptional activation of NFAT is determined by electrophoretic mobility shift assay similar to that described by Yang et al., *J Biol Chem.* 2000; 275:4541-4. Preincubation of the same cells with 5 micromolar of the test compound for 2 hours prior to addition of an activator of NFAT inhibits the activation of NFAT otherwise observed in the absence of said compound.

Example 5: Method for Screening for Compounds that Modify the Activity of PPARgamma and PPARalpha based on Inhibition of IL-2 production

[0255] Isolated human T lymphocytes or a mammalian cell line such as a Jurkat T cell line transfected with the PPARalpha and/or the PPARgamma expression vector is stimulated with a concentration of one or a combination of PHA/PMA, TNF-alpha, interferon-gamma or some other factor that activates induction of IL-2 gene expression. Production of IL-2 is determined measuring the concentration of IL-2 in the supernatant

from cells using Endogen kits (Wolburn), as described by Yang et al., *J. Biol. Chem.*. 2000; 275:4541-4. Preincubation of the same cells with 5 micromolar of the test compound for 12 hours prior to addition of an activator of IL-2 production inhibits the activation of IL-2 production otherwise observed in the absence of said compound.

Example 6: Methods of determining the anti-apoptotic effect of PPAR ligands in PPARalpha and/or PPARgamma-expressing cells

[0256] In human peripheral T lymphocytes from normal healthy donors or a mammalian cell line such as a Jurkat T cell line transfected with the PPARalpha and/or the PPARgamma expression vector, apoptosis (cell death) is induced by adding TNF-alpha (10 ng/ml) and interferon(INF)-gamma (10 ng/ml) (Genzyme, USA). The inhibitory activity of a test compound in preventing this apoptosis is determined by using dexamethasone as the standard, a compound known to have apoptosis inhibitory activity. An aliquot of RPMI-1640 culture medium (containing 10 weight % of fetal bovine serum) is added to each well of a 96-well microplate. Then a test solution of the candidate compound in dimethylsulfoxide is added to the culture medium to give the desired final concentration (0.1 to 10 micromolar). Subsequently, TNF-alpha (40 ng/ml, final concentration) and INF-gamma (10 ng/ml) are added to the culture medium, and cells incubated for 72 hours at 37 degree C in the presence of 5% carbon dioxide in air. After cultivation, the culture medium is removed from wells by aspiration, and 50 microliter of a 5%(w/v) crystal violet/70%(v/v) methanol solution added to each well to stain living cells. The wells are washed and dried and apoptosis inhibitory activity of the test compound is obtained by determining the optical density by using an absorptiometer [Microplate Reader Model 450, produced by Bio-Rad] at the wavelengths of 570 nm. Dexamethasone standard is compared to the test compound at a final concentration of 1 micromolar.

Example 7: Treatment of Primary or Secondary Glaucoma and Glaucomatous Retinopathy by Oral Administration of a Compound of this Invention: - A Clinical Trial

[0257] Early disease: A patient having early ophthalmic manifestations of glaucoma and increased intra-ocular pressure is selected for therapy. The patient weighs 70 kilograms, and if female of child-bearing capacity, is given a pregnancy test to confirm that she is not pregnant. Provided that the patient is not pregnant and does not plan to become pregnant during treatment, a compound of this invention is screened and it's ED50 for PPAR subtypes determined. Using the mathematical algorithm described above, a therapeutically efficacious dose is selected by one skilled in the art. The patient is evaluated by an ophthalmologist experienced in the ophthalmic manifestations of glaucoma and glaucomatous lesions. Regression of the disease or improvement in his clinical status is evaluated by monitoring intraocular pressure, visual fields, and visual reflexes. For more intractable or recalcitrant cases, the daily oral dose is increased about 1 to 3 fold. Additionally, a complete blood count, including white cell count and differential, a platelet count, and liver function tests (such as levels of alkaline phosphatase, lactate dehydrogenase, and aminotransferases) are checked prior to treatment and monthly thereafter. The selected dosage is continued, depending on the response to therapy. The dose may be tapered to a lower (maintenance) dose, again depending on the response to therapy.

[0258] Late disease: A similar patient with late ophthalmic manifestations of chronic glaucoma, in particular, with retinal manifestations including maculopathy, retinopathy and retinal ischemia, is selected for therapy. The approach is the same as for the foregoing patient, except that the starting doses are generally higher.

Example 8: Treatment of Optic Neuritis, or a Retinitis, or a Retinopathy, or Macular Degeneration by Oral Administration of a Compound of this Invention - A Clinical Trial

[0259] Early disease: A patient having early ophthalmic manifestations of retinitis pigmentosa is selected for therapy. The patient weighs 70 kilograms, and if female of

child-bearing capacity, is given a pregnancy test to confirm that she is not pregnant. Provided that the patient is not pregnant and does not plan to become pregnant during treatment, a compound of this invention is screened and it's ED50 for PPAR subtypes determined. Using the mathematical algorithm described above, a therapeutically efficacious dose is selected by one skilled in the art. The patient is evaluated by an ophthalmologist experienced in the ophthalmic manifestations of retinitis pigmentosa lesions. Regression of the disease or improvement in his clinical status is evaluated by monitoring the visual fields. Additionally, a complete blood count, white cell count and differential, a platelet count, and liver function tests (such as levels of alkaline phosphatase, lactate dehydrogenase, and aminotransferases) are checked prior to treatment and monthly thereafter. The dosage is tapered to a maintenance dose of 4 mg.

[0260] Late disease: A similar patient with late ophthalmic manifestations of retinitis pigmentosa is selected for therapy. The approach is the same as for the foregoing patient, except that the doses are generally higher. After 12 months, the dose is decreased to a lower (maintenance) dose of 4 mg or 8 mg once daily.

Example 9: Therapy for Preventing Acute and Chronic Allograft Rejection - A Clinical Trial

[0261] A patient who is a candidate for kidney, liver or heart transplantation or other form of organ transplantation is selected for a therapy. The patient may or may not be receiving other therapies for transplant rejection. A compound of this invention, referred to as the test drug, is orally administered in a dosage effective to achieve suppression of T cell activation as known to those with skill in the art. Using the mathematical algorithm described above, a therapeutically efficacious dose is selected by one skilled in the art. Therapy is initiated 2 weeks prior to transplantation. Within 24 to 48 hours post-operatively, therapy with the test drug is resumed and the patient is monitored for changes in symptoms and signs consistent with acute (usually occurring within days) or chronic (within 2 to 6 months) rejection, as known to a practitioner skilled in the art of managing post-transplantation allograft rejection/survival. Additionally, a complete blood

count, including white cell count and differential, a platelet count, and plasma IL-2 levels, serum creatinine and BUN levels, liver function tests (such as levels of alkaline phosphatase, lactose dehydrogenase, and transaminases), lipid profile, blood glucose, urinary protein and other tests or evaluations known to a practitioner skilled in the art of managing post-transplantation allograft rejection/survival, are checked prior to allograft transplantation, immediately post-operatively (for monitoring acute rejection) and periodically thereafter for the ensuing months, up to 6 months (for monitoring chronic rejection). Administration of a compound of this invention prevents or decreases signs or symptoms of allograft rejection. The administration of the therapy also enables the clinician to decrease the dose of other conventionally used immunosuppressive agents without increasing the risk of allograft rejection. The patient experiences fewer side effects associated with the other conventional immunosuppressive agents.

Example 10: A Clinical Trial, Synergistic (Adjunctive) Therapy for Preventing Acute and Chronic Allograft Rejection

[0262] The balance between acute rejection and infection after transplantation continues to be of significant clinical concern, especially during the early post-transplantation period. Acute rejection is a significant risk factor for chronic rejection, and chronic rejection is an important cause of late graft loss. Monoclonal antibodies that selectively block the interleukin-2 receptors on activated T-helper cells are used for immunoprophylaxis or anti-lymphocyte globulins for induction therapy to provide reduced dosing of cyclosporine A throughout the early post-transplantation course.

[0263] In the context of the present invention, a PPARgamma agonist, or a PPARgamma/PPARalpha co-agonist of this invention is used as effective adjunctive therapy for preventing acute and chronic allograft rejection. The PPARgamma agonist is useful for providing reduced dosing of immunosuppressive therapy, including cyclosporine A, tacrolimus, azathioprine, mycophenolate or other related therapy to preventing allograft rejection throughout both early and late phases post-transplantation. The PPARgamma agonist is used with one or more anti-rejection drug, or in combination

with a RXR agonist, or a PPARgamma/RXR agonist, and/or a vitamin D receptor agonist, and/or a glucocorticoid receptor agonist, and/or an estrogen receptor agonist, and/or an androgen receptor agonist.

[0264] To achieve a synergistic effect, the treatment can be modified to include combination therapy with a PPARgamma/RXR heterodimer ligand (a rexinoid) or another immunosuppressive compound traditionally used for preventing allograft rejection. Examples of such compounds that provide for synergistic effect when given in combination with the drugs encompassed by the current invention include ligands for the glucocorticoid nuclear receptor ligand (e.g. prednisone), inhibitors of purine synthesis (e.g. azathioprine and mycophenolate), and inhibitors of the calcineurin-dependent cytokine synthesis in activated lymphocytes (e.g. cyclosporine, tacrolimus, sirolimus). One or a combination of these compounds are employed (at dosages described above in the section on *Dosage and Schedules*) in clinical trials similar to the one described above in Examples 5 and 6, or in doses sufficient to prevent or treat allograft rejection. Examples of synergistic combinations are as follows:

a. A PPARgamma or a PPARalpha/PPARgamma co-activator, both compounds of this invention, is administered in combination with prednisone at an FDA-approved dose.

b. A PPARgamma or a PPARalpha/PPARgamma co-activator is administered in combination with prednisone *and* cyclosporine A or tacrolimus at an FDA-approved dose, or sirolimus at a dose use in clinical trials.

c. A PPARgamma or a PPARalpha/PPARgamma co-activator is administered in combination with prednisone *and* cyclosporine A or tacrolimus or sirolimus, *and* azathioprine or mycophenolate.

d. A PPARgamma or a PPARalpha/PPARgamma co-activator, is administered in combination with one or more FDA-approved immunosuppressive transplant rejection therapeutic compound, as described in examples a, b and c above.

e. A rexinoid PPARgamma/RXR heterodimer ligand (e.g. LG100754) is administered in combination with one or more FDA-approved immunosuppressive transplant rejection therapeutic compound at approved dosages as described in examples a, b and c above.

Example 11: Treatment of Chronic Recalcitrant Multiple Sclerosis by Oral Administration of a Compound of this Invention - A Clinical Trial

[0265] The following is an example for treating individuals with chronic recalcitrant multiple sclerosis with an PPARgamma or a PPARalpha/PPARgamma co-activator. This method also applies to the treatment of relapsing, remitting multiple sclerosis, to prevent recurrent exacerbations of the disease.

[0266] Early disease: The patient presents acutely with the neurological manifestations of multiple sclerosis, and the diagnosis is confirmed by clinical laboratory and pathological diagnostic tests. The patient is evaluated by a neurologist experienced in the clinical and laboratory manifestations of multiple sclerosis lesions. The patient weighs 70 kilograms, and if female of child-bearing capacity, is given a pregnancy test to confirm that she is not pregnant. Provided that the patient is not pregnant and does not plan to become pregnant during treatment, a compound of this invention is screened and it's ED50 for PPAR subtypes determined. Using the mathematical algorithm described above, a therapeutically efficacious dose is selected by one skilled in the art. A compound of this invention is administered daily during the acute episode, and is titrated up 0.5 to 3-fold higher doses at weekly intervals. Regression of the disease or improvement in his clinical status is evaluated by monitoring improvement in motor deficits. Reduction of the systemic inflammation associated with the disease is assessed by performing bi-monthly measurements of high sensitivity-C-reactive protein (hs-CRP). A reduction in the hs-CRP by 50% within 3 months of initiating therapy is considered to be a positive response to the therapy. Additionally, a complete blood count, white cell count and differential, a platelet count, liver function tests (such as levels of alkaline phosphatase, lactate dehydrogenase, and aminotransferases), erythrocyte sedimentation rate and

plasma interleukin-2 levels are checked prior to treatment and monthly thereafter. After 6 months treatment, the dosage is tapered to a lower (maintenance) dose.

Example 12: Combination Treatment of a PPAR-Mediated Inflammatory, Proliferative Dermatological (Skin) Disease with PPARgamma Agonist or a Mixed PPARgamma/PPARalpha Agonist (Co-Ligand) and a Vitamin D Derivative - A Clinical Trial

[0267] The PPAR-mediated disease is an inflammatory, proliferative or degenerative skin disease such as psoriasis, keratitis, hidradenitis, ichthyosis, acne, rosacea, verrucae and other HPV infections, atopic dermatitis, allergic dermatitis, chemical (irritant) dermatitis, seborrheic dermatitis, solar dermatitis, acute and chronic eczema, seborrheic keratosis, senile keratosis, actinic keratosis, photo-induced keratosis, skin aging, thinning skin, dry skin, wrinkle formation, photo-induced skin aging, keloids, lichen planus.

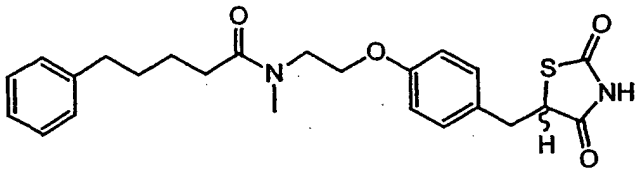
[0268] The PPARgamma agonist or mixed PPARgamma/PPARalpha agonist of this invention is administered at doses consistent with the EC50 for PPARalpha and PPARgamma, and with the pharmacokinetic area under the curve (AUC), and is given as a once or twice daily oral dose, or in a pharmaceutical composition for topical administration, with active ingredient at a concentration ranging from 0.01 to 2.0%, 0.25% of the preferred PPAR agonist are selected. An orally administered vitamin D derivative is selected from: dihydrotachysterol (1 mg daily), 1,25-dihydroxycholecalciferol (1 mcg daily), 25-hydroxycholecalciferol (0.1 mg daily), ergocholecalciferol (1.25 mg daily), and cholecalciferol (1 mg daily). Synthetic vitamin D derivatives are administered topically and is selected from the group consisting of calcipotriene and calcitriol (both at a concentration of 0.005% in an ointment or lotion or shampoo). These pharmacological compositions may be used to treat acute or chronic disease or may be used prophylactically to prevent the onset of the disease.

Example 13: Use of Compounds of this Invention as Synergistic (Adjunctive) Therapy in the Treatment of a Neuro-Degenerative Disease or an Autoimmune Disease - A Clinical Trial

[0269] Multiple sclerosis is the example of the neuro-degenerative, autoimmune disease. Current therapies for MS consist of three interferonbeta preparations (Betaseron, Avonex, and Rebif), Copolymer 1 (Copaxone), and Novantrone. According to this invention, a PPARalpha and/or PPARgamma agonist may be used adjunctively in combination therapy with any of the existing (approved) therapies (identified above) for treating MS. For the purpose of this example, a compound of this invention, a PPARgamma agonist or a PPARgamma/PPARalpha co-agonist, is selected for adjunctive use, and doses are selected as outlined above. The patient presents acutely with the neurological manifestations of multiple sclerosis, and the diagnosis is confirmed by clinical laboratory and pathological diagnostic tests. The patient is evaluated by a neurologist experienced in the clinical and laboratory manifestations of multiple sclerosis lesions. The patient is a male weighing 70 kilograms or a female weighing 50 kilograms and being treated with an interferonbeta preparation, Copaxone, or Novantrone. An adjunctive PPARgamma agonist, or a PPARalpha and PPARgamma co-agonist (co-activator), is selected from the compounds described in this invention. Adjunctive therapy is initiated at one-half the preferred dose as indicated above. The dose is doubled within 6 to 8 wks of initiation of said adjunctive therapy. The patient is monitored for improvement based on laboratory and clinical findings. The regime is continued as medically indicated to one of skill in the art of treating MS.

Example 14 : Synthesis of BP-015

BP-015



5-Phenyl-pentanoic acid {2-[4-(2,4-dioxo-thiazolidin-5-ylmethyl)-phenoxy]-ethyl}-methyl-amide (63)

[0270] To a 100 ml round bottomed flask was added 19 (0.224 g or 0.9mmol), as the hydrochloride salt of 5-({4-[2-(methylamino)ethoxy]phenyl}methyl)-1,3-thiazolidine-2,4-dione, in 30 ml of dry dichloromethane. Triethylamine (0.1 ml or 0.9 mmol) was added at 0 °C and the mixture was stirred at this temperature for an additional 10 minutes. Phenylvaleric acid 6 (0.126 g or 1.0 mmol) was dissolved in 50 ml of dichloromethane in a separate round bottomed flask and was cooled to 0 °C. To this was added triethylamine (0.1 ml or 0.9 mmol) followed by the 5 minute dropwise addition of (0.08 ml) isobutyl chloroformate. The mixture was stirred for an additional 10 minutes at this temperature and the resultant mixed anhydride was tranferred by cannula to the other flask containing the free amine. The combined mixture was stirred at 0 °C for 1 hr. Water was added and the aqueous layer was extracted with 2 X 50 ml of dichloromethane. The combined organic layer was washed with 10% sodium bicarbonate and then with sat. aq. brine. The dichloromethane was removed under vacuum and the residue chromatographed over silica gel with $CHCl_3$ to yield 0.212 g of 63 or BP-015 (68%).

^{1}H-NMR ($CDCl_3$): δ 8.8 (bs, 1H); 7.24 (m, 2H); 7.15 (m, 5H); 6.81 (d, J = 8.6Hz, 2H); 4.5 (dd, J = 3.8Hz, 9Hz, 1H); 4.09 (t, J = 5Hz, 2H); 3.72 (t, J = 5Hz, 2H); 3.45 (dd, J = 3.8Hz, 18Hz, 1H); 3.12 (s, 3H); 3.1 (dd, J = 9Hz, 18Hz, 1H); 2.63 (m, 2H); 2.33 (t, 2H); 1.67(m, 4H).

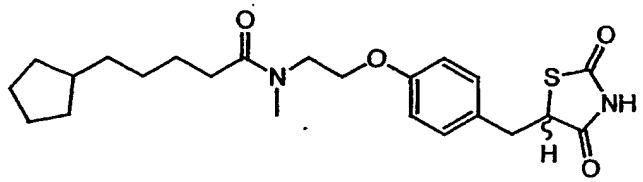
^{13}C-NMR ($CDCl_3$): 24 5 (t); 31.0 (t); 33.2 (t); 33.9 (d); 35.6 (t); 37.3 (q); 37.7 (t); 47.9 (t); 53.6 (d); 66.5 (t); 114.6 (d); 125.6 (d); 128.3 (d); 130.3 (d); 157.9 (s); 171.1 (s); 173.8 (s); 175.0 (s).

HRMS : (Cal for $C_{24}H_{28}N_2O_4S$ 441.1842). Found 441.1793.

IR (Thin Film): 3432, 1751, 1699, 1610, 1244 cm^{-1}.

Example 15 : Synthesis of BP-016, a particular compound of this invention

BP-016



5-Cyclopentyl-pentanoic acid {2-[4-(2,4-dioxo-thiazolidin-5-ylmethyl)-phenoxy]-ethyl}-methyl-amide (20)

[0271] To a 100 ml round bottomed flask was added 19 (0.224 g or 0.9mmol), as the hydrochloride salt of 5-({4-[2-(methylamino)ethoxy]phenyl}methyl)-1,3-thiazolidine-2,4-dione, in 30 ml of dry dichloromethane. Triethylamine (0.1 ml or 0.9 mmol) was added at 0 °C and the mixture was stirred at this temperature for an additional 10 minutes. 5-Cyclopentylvaleric acid 5 (0.120 g or 1.0 mmol) was dissolved in 50 ml of dichloromethane in a separate round bottomed flask and was cooled to 0 °C. To this was added triethylamine (0.1ml or 0.9mmol) followed by the dropwise addition over 5 minutes of 0.08 ml of isobutyl chloroformate. The mixture was stirred for an additional 10 minutes at this temperature and the resultant mixed anhydride was transferred by cannula to the other flask containing the free amine. The mixture was stirred at 0 °C for 1 hr. Water was added and the aqueous layer was extracted with 2 X 50 ml of dichloromethane. The combined organic layer was washed with 10% sodium bicarbonate and then with sat. aq. brine. The dichloromethane was removed under vacuum and the residue chromatographed over silica gel with $CHCl_3$ to yield 0.252 g of 20, or BP-016 (78%).

^{1}H-NMR ($CDCl_3$): δ 9.4 (bs, 1H); 7.13 (d, J = 8.5Hz, 2H); 6.82 (d, J = 8.5Hz, 2H); 4.5 (dd, J = 3.8Hz, 9Hz, 1H); 4.08 (t, J = 5Hz, 2H); 3.71 (t, J = 5Hz, 2H); 3.45 (dd, J = 3.8Hz, 18Hz, 1H); 3.13 (s, 3H); 3.1 (dd, J = 9Hz, 18Hz, 1H); 2.31 (t, J = 7.4, 2H); 1.71(m, 3H); 1.62 (m, 7H); 1.31 (t, J = 4.5Hz, 4H); 1.1 (m, 2H)..

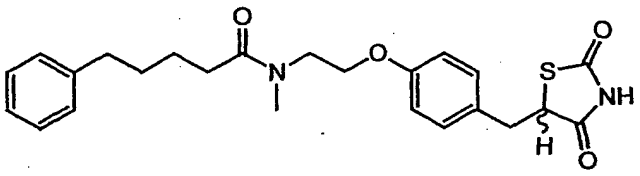
^{13}C-NMR ($CDCl_3$): 25 0 (t); 25.5 (t); 28.4 (t); 28.5 (t); 32.5 (t); 33.4 (t); 33.9 (d); 35.7 (t); 37.5 (q); 37.7 (t); 39.8 (t); 47.8 (t); 53.6 (d); 66.5 (t); 114.6 (d); 128.2 (s); 130.3 (d); 157.9 (s); 170.9 (s); 173.9 (s); 174.8 (s).

HRMS: (Calc for $C_{23}H_{32}N_2O_4S$ 433.2155). Found 443.2153.

IR (Thin Film): 3432, 2943, 1752, 1701, 1610, 1512, 1245 cm^{-1}.

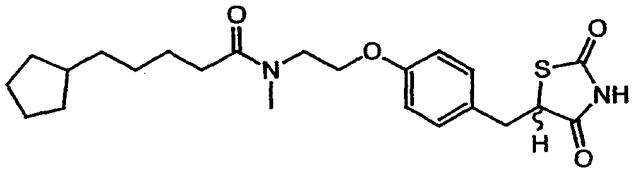
Example 16: Assay of the compounds ability to activate PPARs

BP-015



5-Phenyl-pentanoic acid {2-[4-(2,4-dioxo-thiazolidin-5-ylmethyl)-phenoxy]-ethyl}-methyl-amide (63)

BP-016



5-Cyclopentyl-pentanoic acid {2-[4-(2,4-dioxo-thiazolidin-5-ylmethyl)-phenoxy]-ethyl}-methyl-amide (20)

[0272] The ability of representative compounds of this invention to activate PPARgamma was tested in a FRET assay in vitro system using standard methods familiar

to those skilled in the art. The following Table shows the EC50s for activation of the various PPAR isoforms of the following compounds of the current invention.

Table A. EC50s for PPAR isoforms by Compounds of this invention

Compound	EC50 for PPAR isoforms
Cyclopentyl BP 16	PPARgamma < 10 nanomolar PPARalpha = 720 nanomolar PPARdelta > 10 micromolar
Phenyl BP 15	PPARgamma < 10 nanomolar PPARalpha = 2.1 micromolar PPARdelta > 10 nanomolar

[0273] These findings demonstrate that representative compounds of this invention are extremely potent activators of PPARgamma. Because many thiazolidinediones and non-thiazolidinediones do not activate PPARgamma, the current results are surprising. Moreover, the compounds are significantly more effective in activating PPARgamma than rosiglitazone, the most potent ligand for PPARgamma approved for clinical use in the United States. Compounds that activate PPARs are known to be effective in the treatment of a variety of disorders involving alterations in cell proliferation, inflammation, and or disturbances in carbohydrate or lipid metabolism. Thus, the compounds of this invention will have utility for treating and preventing type II diabetes, hypertension, atherosclerosis, restenosis after angioplasty, psoriasis, various malignancies, rheumatoid arthritis, asthma, chronic obstructive pulmonary diseases and other clinical disorders that may be affected by activation of PPARs as described in this document. Because the compounds of the invention are potentially more potent in activating PPARgamma than rosiglitazone, they represent a significant improvement for the treatment of clinical disorders for which rosiglitazone might be used as therapy. Because of the extensive homology between PPARgamma and other isoforms of PPAR (PPARalpha and PPARdelta), the compounds of this invention also may be useful for the treatment of clinical disorders influenced by either PPARalpha or PPARdelta or both.

Example 17: Use of a compound of this invention to treat a metabolic and/or inflammatory disease

[0274] This example illustrates a clinical trial and therapy by oral administration. A patient having type 2 diabetes mellitus, or a dyslipidemia (e.g. hypercholesterolemia or hypertriglyceridemia), or chronic generalized psoriasis, with or without psoriatic arthritis, or rheumatoid arthritis, or inflammatory bowel disease (e.g., ulcerative colitis) is selected for therapy. The patient weighs 80 kilograms. For infants or children the doses suggested are lowered in a linear fashion based on body weight or surface area. The female patient of child-bearing potential is given a pregnancy test to confirm that the patient is not pregnant. Provided that the patient is not pregnant and does not plan to become pregnant during treatment, according to this invention, a PPARgamma agonist or a PPARgamma partial agonist (SPARM) or a PPARalpha/PPARgamma dual agonist or a PPARalpha/PPARgamma partial agonist, or a PPARgamma/PPARdelta dual agonist is orally administered in a dosage of 0.1 to 500 milligrams once or twice daily, more typically 2 to 25 mg once or twice daily. The patient is monitored for improvement in the manifestations of the index disease. Additionally, a complete blood count, including white cell count and differential, a platelet count, and liver function tests (such as levels of alkaline phosphatase, lactose dehydrogenase, and transaminases) are checked prior to treatment and periodically thereafter. The dosage is maintained or tapered when the manifestations of the disease subside, as judged by one skilled in the art of medicine.

[0275] Tables I through X provides further examples of diseases or disorders treatable with methods described in this invention:

TABLE I: Examples of dermatological disorders treatable using compounds described in this invention

Kertinizing skin diseases, keratitis, hidradenitis, ichthyosis
Psoriasis (all forms, including p. vulgaris, p. guttata, p. discoidea, p. anthropica, p. universalis)
Acne (all forms, including a. vulgaris, a. rosacea, a. inversa, cystic acne)
Warts, verruca (all forms, including common warts, anogenital (venereal) warts, viral warts including human papilloma virus (HPV) infections, conjunctival warts, oral/buccal warts)
Acute and chronic dermatitides (inflammation of the skin), atopic dermatitis, allergic dermatitis, contact dermatitis, cosmetic dermatitis, chemical dermatitis, seborrheic dermatitis, solar dermatitis, acute and chronic eczema, diaper rash, sunburn
Lupus associated skin lesions
Keratoses such as seborrheic keratosis, senile keratosis, actinic keratosis, photo-induced keratosis, skin aging, thinning skin, dry skin, wrinkle formation, photo-induced skin aging, keratosis follicularis
Keloids and prophylaxis against keloid formation
Leukoplakia, lichen planus
Urticaria, pruritus
Androgenic alopecia in men and women, hirsutism in women

TABLE II: Examples of psychiatric disorders treatable using compounds described in this invention

Depression, primary depression or depression secondary to chronic diseases and medications
Dysphoric mood disorders
Obsessive compulsive disorder
Dysthymic disorders
Manic depressive (unipolar or bipolar) disorder
Anxiety states including panic disorder and agoraphobia
Post menstrual syndrome
Schizophrenia
Chronic fatigue syndrome
Substance abuse and drug addiction
Anorexia nervosa and anorexia bullemia

TABLE III: Examples of neurological/neurodegenerative disorders treatable using compounds described in this invention

Migraine headaches (e.g. vascular headaches, common migraine)
Primary (e.g. Alzheimer's disease) and secondary (e.g. HIV-related) dementias
Degenerative CNS diseases (e.g. Parkinson's disease, amyotropic lateral sclerosis)
Demyelinating diseases (e.g.multiple sclerosis, Guillain-Barre syndrome)
Pain disorders including algesia, hyperalgesia, acute and chronic pain, allodynia
Primary and secondary encephalitis and encephalomyelitis (e.g. autoimmune encephalomyelitis, allergic encephalomyelitis)
Primary and secondary neuritis, autoimmune neuritis
Other autoimmune diseases (e.g. myesthenia gravis, Eaton-Lambert syndrome)
Congenital and secondary ataxias

TABLE IV: Examples of inflammatory and metabolic disorders associated with allograft transplantation treatable using compounds described in this invention

The compounds described herein are useful as monotherapy or adjunctive therapy with existing immunosuppressive agents for the promotion and maintenance of allograft survival, post-transplantation.

Examples of inflammatory and proliferative conditions or diseases associated with allograft transplantation and immune suppression include:

1. Acute allograft rejection
2. Chronic allograft rejection
3. Graft versus host disease
4. Post-transplantation de novo malignancy (e.g. lymphoma and epidermal cancers)
5. Osteoporosis and osteopenia
6. Hyperlipidemia
7. Insulin resistance and diabetes mellitus
8. Hypertension
9. Atherosclerosis
10. Endarteritis associated with heart allograft transplantation
11. Glomerulonephritis associated with renal allograft transplantation
12. Cardiomyopathy and congestive heart failure associated with allograft transplantation, in particular heart transplantation

TABLE V: Examples of diseases of various organ systems treatable using compounds described in this invention

Organ System	*Disease/Pathology*
Cardiovascular	Hypertension, vasculo-occlusive diseases including atherosclerosis, arteritis, endarteritis, endocarditis, myocarditis, arterial plaque (fibrous cap) rupture, thrombosis, restenosis after any invasive vascular procedures; acute coronary syndromes such as unstable angina, myocardial infarction, myocardial ischemia and other ischemic cardiomyopathies, non-ischemic cardiomyopathies, post-myocardial infarction cardiomyopathy and myocardial fibrosis, drug-induced cardiomyopathy.
Endocrine	Obesity, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, impaired glucose tolerance, Cushing's syndrome (e.g. secondary to chronic glucocorticoid therapy), polycystic ovarian syndrome, osteoporosis, osteopenia, accelerated aging of tissues and organs, e.g. Werner's syndrome.
Urogenital	Prostatitis, endometritis, endometriosis, benign prostatic hypertrophy, leiomyoma, polycystic kidney disease (e.g. autosomal dominant PKD), acute tubular necrosis, nephrotic syndrome, diabetic nephropathy, glomerulonephritis, erectile dysfunction in men and women.
Pulmonary	Asthma, chronic obstructive pulmonary disease (COPD), reactive airway disease, pulmonary fibrosis, pulmonary hypertension.
Connective tissue Joint	Rheumatoid arthritis, Raynaud's phenomenon/disease, Sjogren's syndrome, systemic sclerosis, systemic lupus erythematosus, inflammatory bowel disease (ulcerative colitis, Crohn's disease) vasculitides, ankylosing spondylitis, osteoarthritis, reactive arthritis, psoriatic arthritis, fibromyalgia, osteoarthritis, sarcoidosis.
Liver/Other	Hepatic fibrosis, hepatic cirrhosis, hepatic steatosis, all etiologies, e.g. alcohol-induced (e.g. ethanol), drug-induced (e.g. tylenol), and toxin-induced (e.g. mushroom poisoning) Fibrocystic breast disease, fibroadenoma

TABLE VIa: Examples of neoplastic diseases treatable using compounds described in this invention

Organ System	*Malignancy/Cancer type*
Skin	Basal cell carcinoma, melanoma, squamous cell carcinoma; cutaneous T cell lymphoma; Kaposi's sarcoma.
Hematological	Acute leukemia, chronic leukemia and myelodysplastic syndromes.
Urogenital	Prostatic, renal and bladder carcinomas, anogenital carcinomas including cervical, ovarian, uterine, vulvar, vaginal, and those associated with human papilloma virus infection.
Neurological	Gliomas including glioblastomas, astrocytoma, ependymoma, medulloblastoma, oligodendroma; meningioma, pituitary adenoma, neuroblastoma, craniopharyngioma.
Gastrointestinal	Colon, colorectal, gastric, esophageal, mucocutaneous carcinomas.
Breast	Breast cancer including estrogen receptor and progesterone receptor positive or negative subtypes, soft tissue tumors.
Metastasis	Metastases resulting from all neoplasms.
Other	Angiomata, angiogenesis associated with the neoplasms.

TABLE VIb: Examples of neoplastic diseases treatable using compounds described in this invention (cont'd)

Location	*Malignancy/Cancer type*
Various	fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, enthotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelimoa, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, and retinoblastoma.

TABLE VII: Examples of viral infections and related pathologies treatable according to the methods of this invention

VirusViral infection/cancer or other virus-associated pathology	
HTLV	T-cell leukemia/lymphoma, HTLV-associated arthritides/myelopathies.
HPV	Cervical and anogenital cancers; common and anogenital (venereal) warts, including verrucae, condyloma or condyloma acuminata, related non-neoplastic (e.g., keratitis, conjunctivitis) pre-neoplastic and neoplastic (e.g., conjunctival epithelial neoplasms) diseases of the eye.
HAV, HBV, HCV	Hepatitis, hepatocellular carcinoma, lymphoma.
CMV	Hepatitis, retinitis, meningitis.
HSV, VSV	Related mucocutaneous, oropharyngeal and genital diseases, related skin and respiratory infections, varicella-zoster, chicken pox, herpes zoster, post-herpetic neuralgia, conjunctivitis, keratoconjunctivitis, keratitis.
HHV	Exanthem subitum, infectious mononucleosis.
EBV	Infectious mononucleosis, chronic fatigue syndrome, lymphoma, conjunctivitis, keratitis, and related infections of the eye.
Adenoviruses	Upper and lower respiratory tract infections, pneumonia, conjunctivitis.
RSV	Upper and lower respiratory tract infections, pneumonia.
PMV	Mumps and related manifestations, e.g., conjunctivitis.
MV, RV	Measles, Rubella ("German measles") and related manifestations.
Coxsackie viruses	Conjunctivitis, diabetes mellitus, respiratory infections.
Influenza viruses	Upper and lower respiratory tract infections, pneumonia.

HIV, Human Immunodeficiency Virus; HTLV, Human T-cell Lymphocyte Virus; HPV, Human Papilloma Virus; HAV, Hepatitis A Virus; HBV, Hepatitis B Virus; HAV, Hepatitis C Virus; CMV, Cytomegalovirus; HSV, Herpes Simplex Virus (Types I & II); HHV, Human Herpes Virus; EBV, Epstein-Barr Virus; RSV, Respiratory Syncytial Virus; VZV, Varicella-Zoster Virus; PMV, Paramyxovirus; MV, Measles (Rubeola) Virus; RV, Rubella Virus

Table VIII: HIV related infections and diseases treatable using compounds described in this invention

Organ system	*Viral infection/manifestation or other HIV-associated disease*
Immunologic	AIDS, primary HIV infection.
Dermatological	Anogenital cancers including rectal and cervical cancer, Kaposi's sarcoma, atopic dermatitis, squamous cell carcinoma, hairy leukoplakia, molluscum contagiosum, warts (HPV infections), seborrheic dermatitis, psoriasis, xeroderma, HSV and varicella-zoster infections.
Hematologic	Non-Hodgkin's lymphoma, B cell lymphoma, anemia, neutropenia, thrombocytopenia.
Gastrointestinal	Anorexia, gastroparesis, diarrhea, malabsorption, gastrointestinal CMV infections, esophagitis, colitis, hepatitis, lymphoma.
Ophthalmic	Conjunctivitis, keratitis, keratoconjunctivitis, uveitis, retinitis, chorioretinitis, CMV retinitis, iridocyclitis, vitreitis, choroiditis, papilledema, Kaposi's sarcoma, lymphoma, ocular palsies, conjunctival warts, pre-neoplastic and neoplastic diseases of the eye.
Cardiac	Myocarditis, endocarditis, pericarditis.
Pulmonary	CMV pneumonitis, lymphoid interstitial pneumonitis.
Nephrologic	HIV nephropathy, renal cell carcinoma, amyloidosis, uropathy.
Rheumatologic	Arthralgia, fibromyalgia, Reiter's syndrome, psoriatic arthritis, vasculitis.
Neurologic	Dementia, viral meningitis, viral encephalitis, HIV encephalopathy, progressive multifocal leukoencephalopathy, CNS lymphoma, peripheral and autonomic neuropathies.
Psychiatric	Dysphoric mood disorders, depression, depression associated with chronic diseases and medications, bipolar disorder, anxiety disorders, chronic fatigue syndrome, chronic pain, psychoses, substance abuse disorders and drug addiction.
General	Lymphoma, metastatic lymphoma, Kaposi's sarcoma, wasting syndrome, psychosis.

TABLE IXa: Diseases of the eye treatable using compounds described in this invention

1. Inflammatory eye diseases associated with viral infections

Disease	*Virus*
Blepharitis	HSV, VZV, Vaccinia, HPV, molluscum contagiosum
Conjunctivitis	HSV, VZV, EBV, Adenovirus, Vaccinia, Variola, HPV, molluscum contagiosum, influenza
Follicular c.	Newcastle, measles, mumps, rubella, molluscum contagiosum
Hemorrhagic c.	Enterovirus, coxsackie
Catarrhal c	Rubella
Keratitis	HSV, VZV, EBV, Adenovirus, Vaccinia, Variola, HPV, molluscum contagiosum
Keratoconjunctivitis	HSV, VZV, EBV, Adenovirus, Vaccinia, Variola, HPV, molluscum contagiosum
Retinitis	CMV
Uveitis	HPV
Conjunctival warts	HPV
C.epithelial neoplasms	HPV

2. Oularplastic diseases

Benign tumors:	Keratocanthoma, molluscum contagiosum, dermoid cysts, neurofibroma, neurofibromatosis, schwannoma (neurilemoma), pleiomorphic adenoma
Malignant tumors:	Basal cell carcinoma, squamous cell carcinoma, mucoepidermoid carcinoma, melanoma, retinoblastoma, embryonal rhabdomyosarcoma, meningioma, adenoid cystic carcinoma, lymphoid tumors of the orbit, mesenchymal tumors (fibrous hystiocytoma) of the orbit, nasopharyngeal carcinoma.
Vascular lesions:	Hemangioma, lymphangioma.

TABLE IXb: Ophthalmic diseases treatable using compounds described in this invention (cont'd)

*Disease Category/Examples of Diseases, Causes or Associated Conditions**	
Conjunctivitis	Acute allergic conjunctivitis (e.g. drug-related inflammation, hypersensitivity reactions), chronic (vernal) conjunctivitis, contact lens-associated conjunctivitis, e.g. giant papillary conjunctivitis, conjunctival ulceration, including ulceration associated with mucous membrane, conjunctival warts
Blepharitis	Inflammatory etiologies, e.g. blepharitis secondary to rosacea
Ophthalmic fibrosis	Steven's-Johnson syndrome with progressive fibrosis and scarring, cicatrization and symblepharon.
Corneal injury	Corneal abrasion or ulceration (e.g. contact lens-related injury), or corneal injury of any etiology*.
Dry eye syndrome	See Table below
	Pterygium, pinguecula
	PemphigoidIncludes ophthalmic pemhigori
	Scleritis/Episcleritis
	Iridocyclitis
	Endophthalmitis
Uveal tract diseases	Including glaucoma (primary and secondary etiologies) Uveitis, uveoretinitis, panuveitis, all etiologies*
Vitreitis, retinitis	e.g. congenital retinitis, retinitis pigmentosa
Infectious retinitis	Viral (e.g. herpes, cytomegalovirus, HIV), tuberculous, syphititic, fungal (e.g. histoplasmosis)
Chorioretinopathies	Chorioretinitis, choroiditis, vitreitis,
Retinopathies	e.g. Diabetic retinopathy, hypertensive retinopathy Maculopathiesage-related-macular degeneration, white dot syndromes
Cataract	Related to diabetes, age, collagen vascular diseases Ocular palsies

*Etiologies of ophthalmic diseases treatable according to the methods of this invention include diseases induced or caused by physical agents (e.g. UV radiation), chemical agents (e.g. acids, caustic solvents) immunological etiologies (e.g. collagen vascular diseases, auto-immune, T lymphocyte-related), infectious agents such as viruses (HSV, CMV, HIV), mycoplasma, tuberculosis, syphilis, fungae (histoplasmosis)

TABLE IXc: Ophthalmic diseases treatable using compounds described in this invention (cont'd) - Etiologies of dry eye syndrome

I. Conditions Characterized by Hypofunction of the Lacrimal Gland:

A. Congenital

Familial dysautonomia (Riley-Day syndrome), aplasia of the lacrimal gland (congenital alacrima), trigeminal nerve aplasia, ectodermal dysplasia

B. Acquired

1. Systemic Diseases, e.g. Sjögren's Syndrome, progressive systemic sclerosis, sarcoidosis, leukemia, lymphyoma, amyloidosis, hemochromatosis,
2. Infection, e.g. mumps
3. Injury, e.g. surgical removal of lacrimal gland, irradiation, chemical burn
4. Medications, e.g. antihistamines, antimuscarinics (atropine, scopolamine), general anesthetics (halothane, nitrous oxide), beta-adrenergic blockers (timolol, practolol), neurogenic, neuroparalytic (facial nerve palsy)

II. Conditions Characterized by Mucin Deficiency

Avitaminosis A, Stevens-Johnson syndrome, ocular pemphigoid, chronic conjuncitivitis (e.g. trachoma), chemical burns, drugs and medications

III. Conditions Characterized by Lipid Deficiency

Lid margin scarring, blepharitis

IV. Defective Spreading of Team Film Caused by the Following:

A. Eyelid abnormalities

1. Defects, colboma
2. Ectropion or entropion
3. Keratinization of lid margin
4. Decreased or absent blinking secondary to: neurologic disorders, hyperthyroidism, contact lens, drugs and medications, herpes simplex keratitis, leprosy, conjunctival abnormalities, pterygium, symblepharon, proptosis

TABLE IXd: Ophthalmic diseases treatable using compounds described in this invention (cont'd) - Non-hereditary and hereditary degenerative diseases

Macular disorders:	All etiologies and manifestations, including age-related macular degeneration, exudative macular degeneration, atrophic macular degeneration, crystalline retinopathies, retinal toxicosis of systemic medications, idiopathic central serous choroidiopathy, macular edema
Retinovascular diseases and retinopathies:	Retinopathy, vasculo-occlusive r., ischemic r., idiopathic r., hypertensive r., proliferative r., diabetic r., vitreoretinopathy, vasculopathies associated with telangiectasias or aneurysms, retinopathies associated with lupus erythematosus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, uveoretinitis or diabetes mellitus, glaucomatous retinopathies
Glaucoma:	All etiologies and manifestations, including primary and secondary open-angle glaucoma, angle-closure glaucoma, glaucoma associated with intraocular inflammation, elevated intraocular pressure associated with acute glaucoma, steroid-induced glaucoma, glaucoma associated with intraocular hemorrhage, pseudoexfoliative syndrome, glaucomatous optic neuropathy and other degenerative changes (e.g. retinopathy) associated with glaucoma
Cataract:	All etiologies and manifestations, including age-related (UV radiation) cataract, cataract associated with systemic diseases such as collagen vascular disease, diabetes mellitus, Wilson's disease
Other diseases:	Primary or secondary retinal detachment

TABLE IXe: Ophthalmic diseases treatable using compounds described in this invention (cont'd) - Congenital degenerative retinopathies

1.	*Primary pigmented retinopathies, all gene types* - Autosomal dominant retinitis pigmentosa, e.g. rod-cone and cone-rod degenerations - Autosomal recessive retinitis pigmentosa, e.g. rod-cone and cone-rod degenerations, Lerner's amaurosis congenita - X-linked recessive pigmented retinopathies, e.g. choroideremia
2.	*Secondary pigmented retinopathies (retinopathies associated with systemic diseases)* - Autosomal dominant pigmented retinopathies, e.g. Paget's disease, Charcot-Marie-Tooth, disease, Steinert's disease, Pierre-Marie syndrome - Autosomal recessive pigmented retinopathies, e.g. diabetes mellitus, mannosidoses, mucopolysccharidoses, Batten's d., Refsum's d., Usher syndrome - X-linked recessive pigmented retinopathies, e.g. Hunter syndrome

TABLE X: Diseases or conditions treatable using compounds described in this invention

I.	*Promote healing in the following clinical situations:*
	Surgical or traumatic wounds to healthy tissues or organs
	Wounds caused by chemical or physical agents, e.g. ulcers caused by caustic or erosive chemicals, pressure sores, etc.
	Wounds associated with disease states, e.g. diabetic ulcers etc.
	Wounds in diseased tissues or organs
II.	*Promote cell survival and prevent apoptosis in neurodegenerative diseases:*
	Alzheimer's disease
	Parkinson's disease
	Amyotrophic lateral sclerosis
	Spinal cord injury or transection secondary to trauma or disease
III.	*Attenuation or arrest of the following conditions or processes:*
	The natural aging of cells and tissues
	Aging induced by chemical or physical agents, e.g. sun-induced skin aging
	Accelerated aging associated with diseases, e.g. Werner's syndrome
IV.	*Vitalization and revitalization of organs and tissues*
	Promoting cell growth and preventing cell death in the aging process
	Promoting therapeutic or non-pathological angiogenesis as a therapeutic approach to treating diseases such as congestive heart failure and cardiomyopathy
	Promoting growth of organs and tissues for repair or transplantation

REFERENCES

[0276] Technical background for the methods of synthesis and therapeutic use of compounds of the present invention are described in the following provisional patent applications, patent applications, patents, published applications and publications:

U.S. Pat. No. 09/520,208
U.S. Provisional Appl. No. 60/157890
U.S. Pat. No. 6,150,371
U.S. Pat. No. 6,103,742
U.S. Pat. No. 6,100,403
U.S. Pat. No. 6,087,385
U.S. Pat. No. 6,087,384
U.S. Pat. No. 6,028,088
U.S. Pat. No. RE36,575
U.S. Pat. No. 6,022,897
U.S. Pat. No. 6,011,036
U.S. Pat. No. 6,011,031
U.S. Pat. No. 6,008,237
U.S. Pat. No. 5,990,139
U.S. Pat. No. 5,985,884
U.S. Pat. No. 5,977,365
U.S. Pat. No. 5,972,970
U.S. Pat. No. 5,972,959
U.S. Pat. No. 5,965,589
U.S. Pat. No. 5,962,470
U.S. Pat. No. 5,952,509
U.S. Pat. No. 5,965,584
U.S. Pat. No. 5,952,356
U.S. Pat. No. 5,939,442
U.S. Pat. No. 5,932,601
U.S. Pat. No. 5,925,656
U.S. Pat. No. 5,910,592
U.S. Pat. No. 5,902,726

U.S. Pat. No. 5,889,032
U.S. Pat. No. 5,889,025
U.S. Pat. No. 5,886,014
U.S. Pat. No. 5,885,997
U.S. Pat. No. 5,869,495
U.S. Pat. No. 5,859,051
U.S. Pat. No. 5,847,008
U.S. Pat. No. 5,843,970
U.S. Pat. No. 5,834,501
U.S. Pat. No. 5,827,865
U.S. Pat. No. 5,824,694
U.S. Pat. No. 5,811,439
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WO 00/008002A1 02/17/2000
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Kliewer SA, et al. *Proc Natl Acad Sci USA.* 1997;94:4318-23.
Buckle DR, et al. *Bioorg Med Chem Lett* 1996; 6:2121-6.
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Kliewer SA, et al. *Recent Prog Horm Res.* 2001;56:239-63.
Gampe RT, et al. *Mol Cell.* 2000;5:545-55.
Barroso I, et al. *Nature.* 1999;402:880-3.
Causevic M, et al. *FEBS Lett.* 1999;463:205-10.
Uppenberg J, et al. *J Biol Chem.* 1998;273:31108-12.
Nichols JS, et al. *Anal Biochem.* 1998;257:112-9.

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Hamann LG. *J Org Chem* 2000; 65:3233-5.
Yanagi, Y., et al., (2000) *Biochem. Cell Biol.* 269, 410-414

[0277] All publications, patents and patent applications referred to herein are herein incorporated by reference into the specification in their entirety for all purposes.

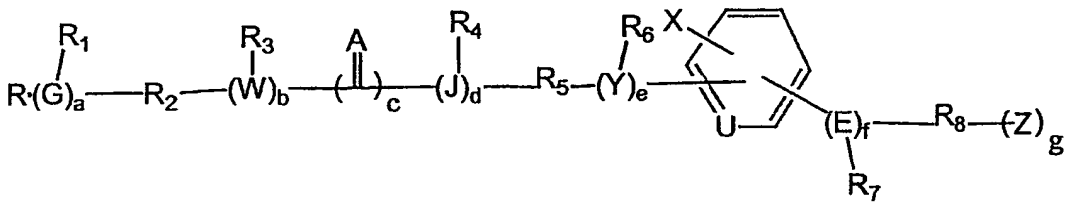
[0278] Although the invention has been described with reference to preferred embodiments and examples thereof, the scope of the present invention is not limited only to those described embodiments. As will be apparent to persons skilled in the art, modifications and adaptations to the above-described invention can be made without departing from the spirit and scope of the invention, which is defined and circumscribed by the appended claims.

[0279] The foregoing is offered primarily for purposes of illustration. It will be readily apparent to those of ordinary skill in the art that the operating conditions, materials, procedural steps and other parameters of the invention described herein may be further modified or substituted in various ways without departing from the spirit and scope of the invention. For example, the invention has been described with human patients as the usual recipient, but veterinary use is also contemplated. Thus, the preceding description of the invention should not be viewed as limiting but as merely exemplary.

CLAIMS

What is claimed is:

1. A compound of Formula 1:



wherein:

a is 0, or 1;

b is 0, or 1;

c is an integer between 0 and 2;

d is 0, or 1;

e is 0, or 1;

f is 0, or 1,

g is 0, or 1;

A is selected from the group consisting of O and S;

R and $R_1 - R_{11}$ is any combination wherein each member of R and $R_1 - R_{11}$ is selected from the group consisting of naught, H, lone pair of electrons, optionally substituted heteroatomic group, alkyl, cycloalkyl, alkylcycloalkyl, arylalkyl, aryl, heteroaryl, heterocyclic, alkylheteroaryl, alkylheterocyclic, and optionally substituted ester, amide, carbonate, or carbamate;

W, G, E or J is selected from the group consisting of O, N, S, $-SO_2-$, $-NHSO_2-$, $-SO_2NH-$, C, C=O, CH, and CH_2;

X is selected from the group consisting of H, halogen, OR_{10}, $NR_{10}R_{11}$, SR, $-SO_2R$, $-SO_2 NR_{10}R_{11}$, and $-NR_{10}SO_2R_{11}$, and further wherein X is attached either *meta* or *para* to the Z containing side chain;

Y is selected from the group consisting of O, N, S, $-SO_2-$,$-NHSO_2-$; $-SO_2NH-$; C, C=O, CH, and CH_2, and further wherein Y is attached either *meta* or *para* to the Z containing side chain;

U is selected from the group consisting of CH, CX, CY, N, and N-oxide;

Z is selected from the group consisting of CO_2R_9, *R* or *S* or racemic 5-substituted-thiazolidine-2,4-dione, *R* or *S* or racemic 3-substituted-pyrrolidine-2,5-dione, 5-substituted-oxazolidine-2,4-dione, 5-substituted-imidazolidine-2,4-dione, 5-substituted-isoindole-1,3-dione, 3-substituted-pyrrole-2,4-dione, 3-Hydroxy-4-substituted-pyrrole-2,5-dione, 4-hydroxy-5-substituted-1,2-dihydropyrazol-3-one, 5-substituted-1,2-dihydro-pyrazol-3-one, 4-substituted-pyrazolidine-3,5-dione, 3-substituted-1H-[1,2,4]triazole, 4-substituted-2H-[1,2,3]triazole, 4-substituted-[1,2,4]triazolidine-3,5-dione, 5-substituted-2,3-dihydro-[1,2,3]triazol-4-one, and 5-substituted-2H-tetrazole.

2. The compound according to claim 1, wherein the point of attachment of Y and X are via carbon atoms in the central ring.

3. The compound according to claim 1, wherein

R1 is a 2, 3, or 4-pyridyl ring;

R is selected from the group consisting of a lone pair of electrons (lpe), H, and substituted or unsubsituted alkyl or aryl group;

G is CH;

b, and f are 0;

a, c, d, g and e are 1;

R2 is selected from the group consisting of -(CH2)6 to -(CH2)2-;

R4 is selected from the group consisting of H, CH3, ethyl, and propyl;

R5 is selected from the group consisting of -(CH2)- to -(CH2)4-;

R6 is selected from the group consisting of a lone pair of electrons (lpe), H, and substituted or unsubsituted alkyl or aryl group;

A is selected from the group consisting of O and S;

J is selected from the group consisting of O, N, and S;

Y is selected from the group consisting of O, N, S, and CH;

X is selected from the group consisting of H, F, Cl, Br, and I;

U is selected from the group consisting of N, and CH;

R8 is selected from the group consisting of CH=CH-, C=O, and CH2;

R9 is selected from the group consisting of H, substituted or unsubstituted alkyl group, and nontoxic metal salt; and

Z is selected from the group consisting of COOR9 and 5-substituted 1,3-thiazolidine-2,4-dione.

4. The compound according to claim 1, further wherein

R_1 is a 4-pyridyl ring;

R is selected from the group consisting of a lone pair of electrons (lpe), H, substituted or unsubsituted alkyl group;

G is CH;

b, and f are 0;

a, c, d, g and e are 1;

R_2 is selected from the group consisting of $-(CH_2)_6$ to $-(CH_2)_4-$;

R_4 is selected from the group consisting of CH_3;

R_5 is selected from the group consisting of $-(CH_2)_2-$ to $-(CH_2)_4-$;

R_6 is selected from the group consisting of lpe, H, and substituted or unsubsituted alkyl group;

A is selected from the group consisting of O and S;

J is selected from the group consisting of O, N, and S ;

Y is selected from the group consisting of O and S;

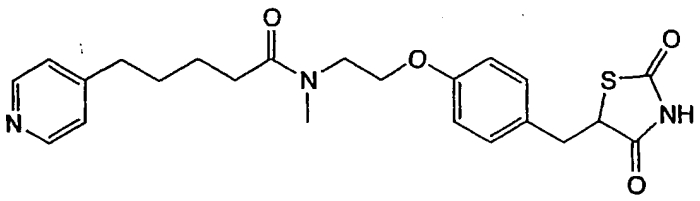
X is selected from the group consisting of H, F, and Cl;

U is CH;

R_8 is CH_2; and

Z is 5-substituted 1,3-thiazolidine-2,4-dione.

5. The compound according to claim 1, wherein the compound is:



6. A pharmaceutical composition comprising a compound of claim 1 or a salt, solvate, ester, tautomer or stereoisomer thereof.

7. The composition of claim 6 further comprising a pharmaceutically acceptable excipient.

8. A method for treating a peroxisome proliferator activated receptor (PPAR) mediated disease, or risk factor, the method comprising administering to a human or an animal in need thereof, a therapeutically effective amount of a compound according to any one of claims 1 - 5.

9. The method according to claim 8, wherein the compound is selected from the group consisting of PPARgamma activator, PPARalpha activator, and PPARdelta activator.

10. The method according to claim 8, wherein the compound is administered in combination with a natural or a synthetic therapeutic compound.

11. A method for designing an L-shaped ligand molecule capable of binding to at least one of PPAR-α, δ, and γ, the method comprising:

(a) identifying at least one ligand binding domain (LBD) in a selected PPAR;

(b) selecting at least a first chemical group capable of binding to the LBD of the PPAR;

(c) selecting a second chemical group capable of interacting with at least one amino acid in the LBD to have an effect on transcription mediated by the PPAR; and

(d) determining a formula of an L-shaped ligand molecule wherein the L-shaped ligand molecule comprises a first leg section and a second leg section, the first leg section comprising the first chemical group that binds the LBD of the PPAR, and the second leg

section comprising the second chemical group which interacts with an amino acid on the PPAR, and further wherein the first and second leg sections of the L-shaped ligand molecule are connected at an elbow atom common to both legs such that the first and second legs are capable of orienting in a conformation which creates an angle of about 80 to 110 degrees between the first and second legs.

12. The method of claim 11, further comprising:

(e) synthesizing the L-shaped ligand molecule and determining its ability to bind to at least one of PPAR-α, δ, and γ.

13. The method of claim 11, wherein the LBD of the PPAR comprises a cysteine residue.

14. The method of claim 13, wherein the first chemical group comprises a thiol which is capable of forming a disulfide linkage with the cysteine residue in the LBD.

15. The method of claim 13, wherein the first chemical group comprises a halogen-substituted pyridine group which which is capable of forming a covalent linkage with the cysteine residue in the LBD.

16. The method of claim 11, wherein the first leg section of the L-shaped ligand molecule comprises a lipophilic terminal group that promotes binding to an active site of a PPAR isoform.

17. The method of claim 11, wherein the interaction of the amino acid of the LBD with the second chemical group on the L-shaped ligand molecule is via hydrogen bonding.

18. The method of claim 11, wherein the L-shaped molecule is an activating ligand that binds the PPAR, and further wherein the second chemical group on the L-shaped ligand molecule interacts with a Tyr473 residue on the PPAR.

19. The method of claim 11, wherein the L-shaped ligand molecule is an inactivating ligand that binds the PPAR, and further wherein the second chemical group on the L-shaped ligand molecule does not interact with a Tyr473 residue on the PPAR.

20. The method of claim 11, wherein the L-shaped ligand molecule is designed for optimal binding to a PPAR LBD by determining at least one geometric constraint on the molecule.

21. The method of claim 11, wherein the L-shaped ligand molecule is an agonist of the PPAR.

22. The method of claim 11, wherein the ligand is an antagonist of the PPAR.

23. A computer-assisted method for designing a L-shaped ligand molecule specific for at least one of PPAR-α, δ, and γ, using a programmable computer including a processor, an input device, and an output device, the method comprising:

(a) inputting into the programmable computer, through the input device, data including the identity of at least one ligand binding domain (LBD) in the selected PPAR;

(b) determining, using the processor, the identity of at least a first chemical group capable of binding to the LBD of the PPAR;

(c) determining, using the processor, the identity of a second chemical group capable of interacting with at least one amino acid in the LBD to have an effect on transcription mediated by the PPAR; and

(d) outputting, to the output device, the formula of an L-shaped ligand molecule wherein the L-shaped ligand molecule comprises a first leg section comprising the first chemical group which binds the LBD of the PPAR, and a second leg section comprising the second chemical group which interacts with an amino acid on a PPAR, and further wherein the first and second leg sections of the ligand molecule are connected at an elbow atom common to both leg sections, such that the first and second leg sections are capable of orienting in a conformation with an angle of about 80 to 110 degrees with respect to each other.

24. The method of claim 23, wherein the L-shaped ligand molecule is designed for optimal binding to a PPAR LBD by determining at least one geometric constraint on the ligand.

25. A method for designing an L-shaped ligand molecule capable of binding to at least one of PPAR-α, δ, γ, the method comprising identifying an L-shaped molecule comprising a first leg section L_1 and a second leg section L_2 wherein the longitudinal axes of L_1 and L_2 are connected by a shared elbow atom c, wherein:

(a) L_1 and L_2 are capable of assuming approximately linear extended conformations wherein L_1 and L_2 are independently each about 9-13 Å in length;
(b) leg sections L_1 and L_2 are connected at the elbow atom c such that the first and second leg sections are capable of orienting in a conformation which creates an angle of about 80 to 110 degrees between the first and second legs;
(c) a terminus of L_1 contains an acidic moiety of pK_a between 4 and 6, and has acceptor atoms capable of hydrogen-bonding; and
(d) a terminus of L_2 contains a moiety selected from the group consisting of a basic moiety, an acidic moiety, functional groups of varying polarity, and a neutral hydrocarbon moiety.

26. The method of claim 25, wherein the angle is about 90 degrees.

27. The method of claim 25, further comprising synthesizing the L-shaped ligand molecule identified by the method of claim 25.

28. The method of claim 27, further comprising testing the L-shaped ligand molecule for an ability to bind at least one of PPAR-α, δ, and γ or PPAR isoforms.

29. The method of claim 25, wherein L_1 and L_2 independently are about 11-12 Å.

30. The method of claim 25, wherein L_1 is 11.1 Å and L_2 is 11.4Å.

31. The method of claim 25, further comprising designing the L-shaped ligand molecule wherein the molecule is capable of assuming a configuration wherein a torsional dihedral angle generated by atoms a-b-c-d, wherein atoms a and b are adjacent connected atoms in

leg section L_1, atom b is connected to elbow atom c, and atom c is connected to atom d in leg section L_2, further wherein:

a dihedral angle between a plane containing the atoms a, b and c and a plane containing the atoms b, c and d is between 45 and 85 degrees; and

a distance from an L_1 head group acid proton to an apex of the dihedral angle is at least about 3.5Å.

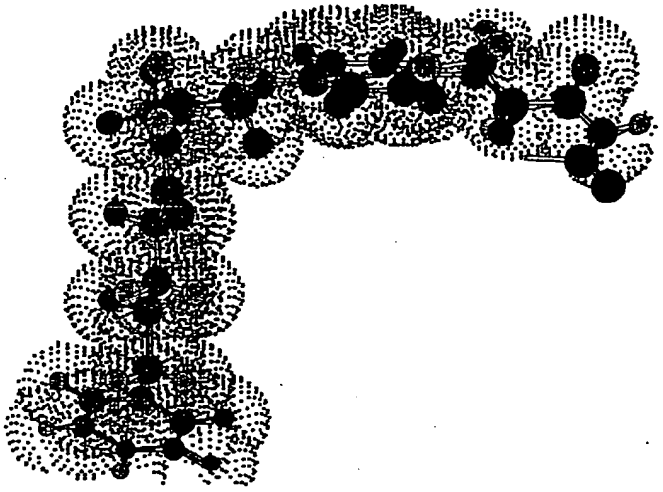


Figure 1

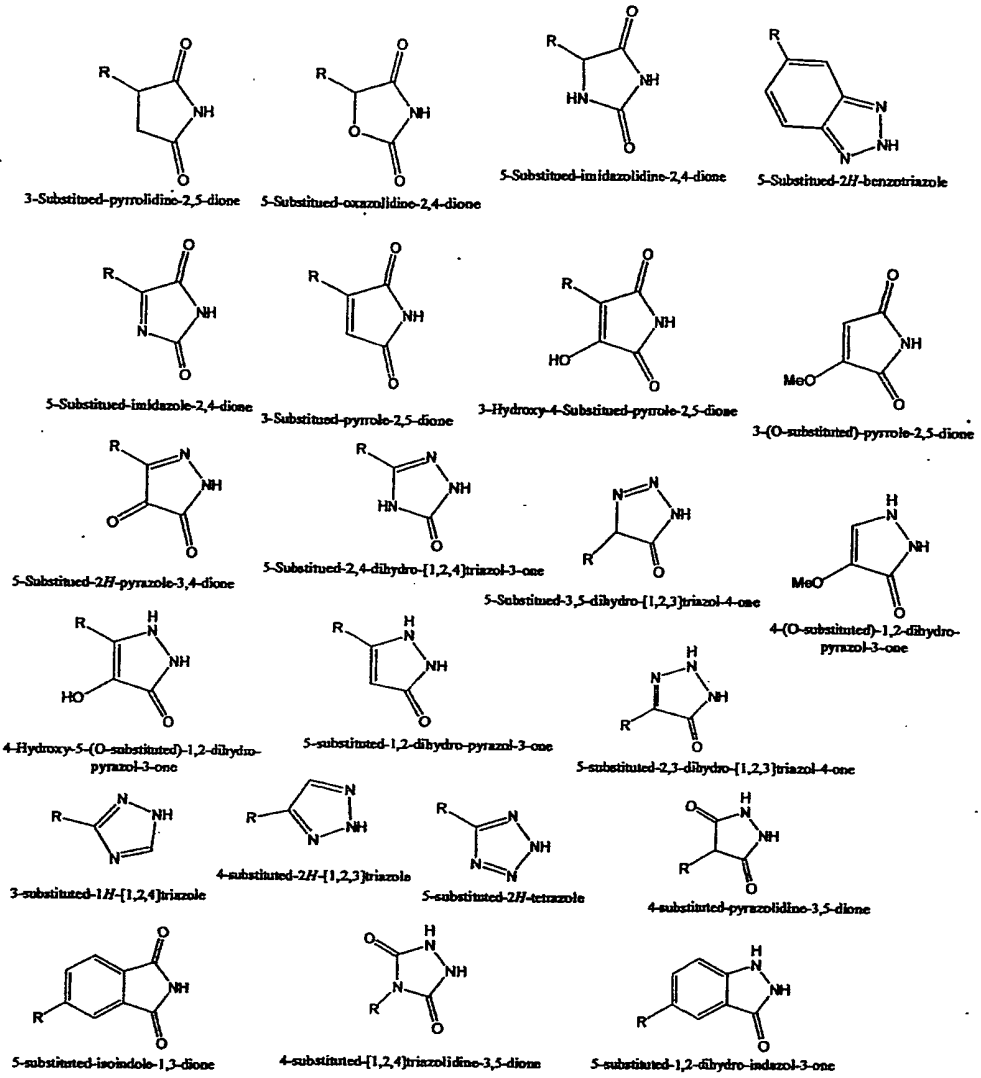

3-Substituted-pyrrolidine-2,5-dione
5-Substituted-oxazolidine-2,4-dione
5-Substituted-imidazolidine-2,4-dione
5-Substituted-2H-benzotriazole
5-Substituted-imidazole-2,4-dione
3-Substituted-pyrrole-2,5-dione
3-Hydroxy-4-Substituted-pyrrole-2,5-dione
3-(O-substituted)-pyrrole-2,5-dione
5-Substituted-2H-pyrazole-3,4-dione
5-Substituted-2,4-dihydro-[1,2,4]triazol-3-one
5-Substituted-3,5-dihydro-[1,2,3]triazol-4-one
4-(O-substituted)-1,2-dihydro-pyrazol-3-one
4-Hydroxy-5-(O-substituted)-1,2-dihydro-pyrazol-3-one
5-substituted-1,2-dihydro-pyrazol-3-one
5-substituted-2,3-dihydro-[1,2,3]triazol-4-one
3-substituted-1H-[1,2,4]triazole
4-substituted-2H-[1,2,3]triazole
5-substituted-2H-tetrazole
4-substituted-pyrazolidine-3,5-dione
5-substituted-isoindole-1,3-dione
4-substituted-[1,2,4]triazolidine-3,5-dione
5-substituted-1,2-dihydro-indazol-3-one

Figure 2

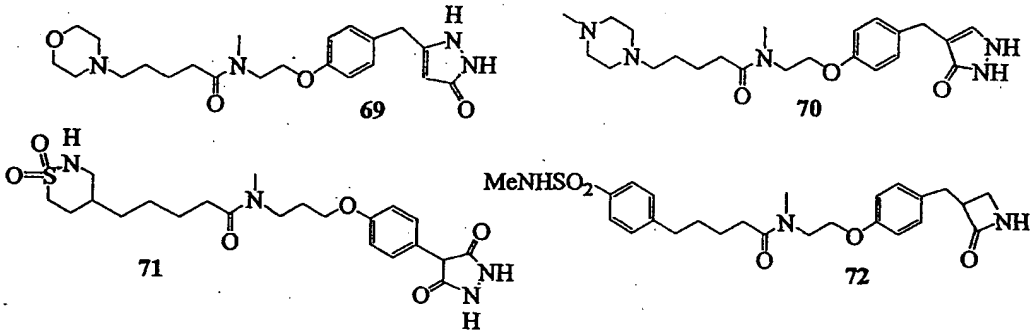


Figure 3

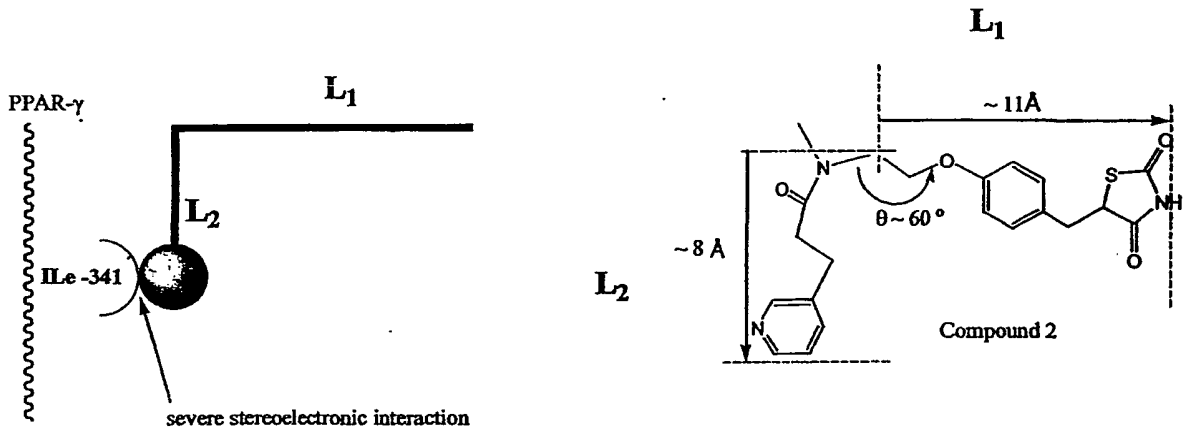
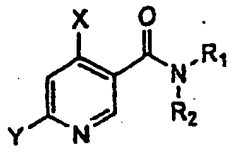
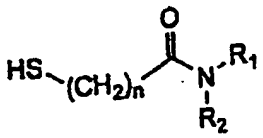

PPAR-γ
L1
L2
ILe -341
severe stereoelectronic interaction
L1
~11Å
~8 Å
L2
θ~60°
Compound 2

Figure 4

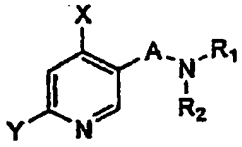
Case 1



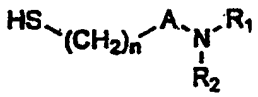
Case 2



Case 3



Case 4



Where R_2 is:

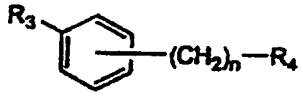
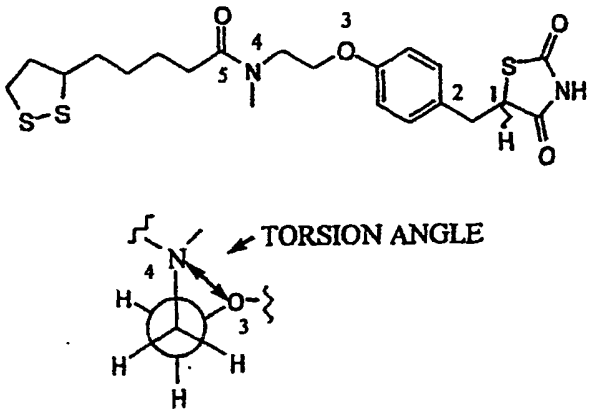
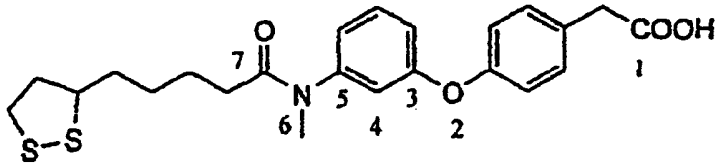


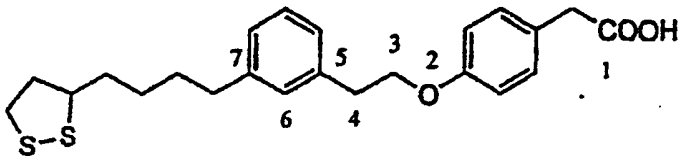
Figure 5



Structure 3



Structure 1



Structure 2

Figure 6